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(54) Title: ANTITHROMBOTIC DIAMINES

(57) Abstract

This application relates to the use as thrombin inhibitors, coagulation inhibitors and thromboembolic disorder agents of diamines of formula (I) as defined herein. It also provides novel compounds of formula (I), processes and intermediates for their preparation, and pharmaceutical formulations comprising the novel compounds of formula (I).

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ANTITHROMBOTIC DIAMINES

This invention relates to thrombin inhibitors which are useful anticoagulants in mammals. In particular it relates to diamine derivatives having high anticoagulant activity, and antithrombotic activity. Thus, this invention relates to new inhibitors of thrombin, pharmaceutical compositions containing the compounds as active ingredients, and the use of the compounds as anticoagulants for prophylaxis and treatment of thromboembolic disorders such as venous thrombosis, pulmonary embolism, arterial thrombosis, in particular myocardial ischemia, myocardial infarction and cerebral thrombosis, general hypercoagulable states and local hypercoagulable states, such as following angioplasty and coronary bypass operations, and generalized tissue injury as it relates to the inflammatory process. In addition, the diamine derivatives are useful as anticoagulants in *in vitro* applications.

The process of blood coagulation, thrombosis, is triggered by a complex proteolytic cascade leading to the formation of thrombin. Thrombin proteolytically removes activation peptides from the Aα-chains and the Bβ-chains of fibrinogen, which is soluble in blood plasma, initiating insoluble fibrin formation.

Anticoagulation currently is achieved by the administration of heparins and coumarins. Parenteral pharmacological control of coagulation and thrombosis is based on inhibition of thrombin through the use of heparins.

Heparins act indirectly on thrombin by accelerating the inhibitory effect of endogenous antithrombin III (the main physiological inhibitor of thrombin). Because antithrombin III levels vary in plasma and because clot-bound thrombin seems resistant to this indirect mechanism, heparins can be an ineffective treatment. Because coagulation assays are believed to be associated with efficacy and with safety, heparin levels must be monitored with coagulation assays (particularly the activated partial thromboplastin time (APTT) assay). Coumarins impede the generation of thrombin by blocking the posttranslational gamma-carboxylation in the synthesis of prothrombin and other proteins of this type. Because of their mechanism of action, the effect of coumarins can only develop slowly, 6-24 hours after administration. Further, they are not selective anticoagulants. Coumarins also require monitoring with coagulation assays (particularly the prothrombin time (PT) assay).

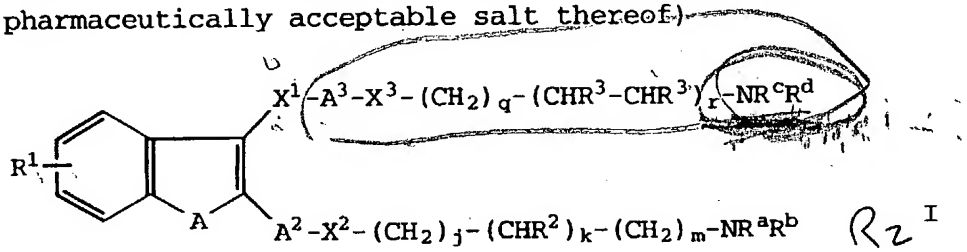
Recently, interest has grown in small synthetic molecules which demonstrate potent direct inhibition of thrombin. See, for example Robert M. Scarborough, Annual Reports in Medicinal Chemistry, (1995), 30, 71-80.

Although the heparins and coumarins are effective anticoagulants, no commercial drug has yet emerged from the small synthetic molecules; and despite the continuing promise for this class of compounds, there still exists a need for anticoagulants which act selectively on thrombin, and which, independent of antithrombin III, exert inhibitory action shortly after administration, preferably by an oral route, and do not interfere with lysis of blood clots, as required to maintain hemostasis.

The present invention is directed to the discovery that the compounds of the present invention, as defined below, are potent thrombin inhibitors that may have high bioavailability following oral administration.

According to the invention there is provided a method of inhibiting thrombin comprising using an effective

amount of a thrombin inhibiting compound of formula I (or a pharmaceutically acceptable salt thereof)



wherein

A is O, S, -CH=CH- or $-CH_2-CH_2-$;

A^2 is an aromatic or heteroaromatic divalent radical selected from para-phenylene, a 6-membered ring heteroaromatic divalent radical containing 1 or 2 ring nitrogens in which the valences are in the 1,4- or 2,5- or 3,6- relationship, and a 5-membered ring heteroaromatic divalent radical containing one oxygen or sulfur ring atom and 0, 1 or 2 ring nitrogens in which the valences are in the 2,5- (or 3,5-) relationship and which divalent radical may bear a (1-3C)alkyl, (1-2C)alkoxy, hydroxy or halo substituent;

A^3 is an aromatic or heteroaromatic divalent radical selected from para-phenylene, a 6-membered ring heteroaromatic divalent radical containing 1 or 2 ring nitrogens in which the valences are in the 1,4- or 2,5- or 3,6- relationship, and a 5-membered ring heteroaromatic divalent radical containing one oxygen or sulfur ring atom and 0, 1 or 2 ring nitrogens in which the valences are in the 2,5- (or 3,5-) relationship and which divalent radical may bear one or two substituents independently selected from (1-4C)alkyl, halo, trifluoromethyl, (1-2C)alkoxy, hydroxy, cyano, aminomethyl, nitro, $-NHCH_2R^f$, $-NHC(O)R^f$ or $-NHS(O)_2R^g$ in which R^f is hydrogen or (1-2C)alkyl and R^g is (1-2C)alkyl or phenyl;

R^1 denotes 0, 1 or 2 substituents on the benz-ring independently selected from halo, methyl, ethyl, hydroxy, methoxy, carbamoyl, aminomethyl and hydroxymethyl;

X^1 is O, S, methylene, carbonyl or ethene-1,1-diyl;

(a) X^2 is imino, a direct bond, methylene, O or S; j is 0; k is 0; m is 1, 2, 3 or 4; provided that when m is 1, then X^2 is a direct bond; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is 2-(hydroxymethyl)-1-pyrrolidinyl, 2-(methoxymethyl)-1-pyrrolidinyl, pyrrolidino, piperidino, 2-methyl-1-piperidinyl, morpholino or hexamethyleneimino; or

(b) X^2 is imino, O or S; j is 1; k is 1; m is 1; R^2 is hydroxy; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is pyrrolidino, piperidino, morpholino or hexamethyleneimino; or

(c) X^2 is imino, O or S; j is 1; k is 1; m is 0; R^2 is hydroxymethyl or methoxycarbonyl; and R^a and R^b are independently hydrogen or (1-3C)alkyl; or

(d) X^2 is imino, O or S; j is 0, 1, 2 or 3; k is 1; m is 0 or 1; provided that j and m are not both 0; R^2 and R^a together form a diradical $-(CH_2)_n-$ in which n is 2, 3 or 4 and the sum of m and n is 3 or 4; and R^b is hydrogen or (1-3C)alkyl; or

(e) X^2 is -NH-C(O)-; j is 0; k is 0; m is 1; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is pyrrolidino, piperidino, morpholino or hexamethyleneimino; and

(1) X^3 is a direct bond, methylene, imino, O or S; q is 0, 1 or 2; and r is 0 or 1; provided that q and r are not both zero, and provided that when q is 1 and r is 0, then X^3 is a direct bond; each R^3 is hydrogen or the two R^3 groups together form a divalent radical $-(CH_2)_s-$ in which s is 3 or 4; and R^c and R^d are independently hydrogen or (1-4C)alkyl or the group NR^cR^d is 2-(hydroxymethyl)-1-pyrrolidinyl, 2-(methoxymethyl)-1-pyrrolidinyl, pyrrolidino, piperidino, morpholino, hexamethyleneimino, 1-imidazolyl or 4,5-dihydro-1-imidazolyl; or

(2) X^3 is imino, O or S; q is 0; r is 1; one R^3 group is (1-5C)alkyl and the other R^3 group is independently hydrogen or (1-5C)alkyl; and R^c and R^d are independently

hydrogen or (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino or hexamethyleneimino; or

(3) X^3 is imino, O or S; q is 0, 1 or 2; r is 1; one R^3 group is hydrogen and the other R^3 group together with the group R^c forms a divalent radical $-(CH_2)_t-$ in which t is 2, 3 or 4 such that the resulting ring is a pyrrolidine or piperidine; and R^d is hydrogen or (1-3C)alkyl; or

(4) X^3 is $-N(R^h)-$; q is 0; r is 1; the R^3 group on the carbon bonded to X^3 and the group R^h together form a diradical $-(CH_2)_3-$; the other R^3 group is hydrogen; and R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino or hexamethyleneimino; or

(5) X^3 is ethene-1,2-diyl or ethyne-1,2-diyl; q is 1; r is 0; and R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino or hexamethyleneimino.

One particular method of inhibiting thrombin comprises using an effective amount of a thrombin inhibiting compound of formula I, or a pharmaceutically acceptable salt thereof, wherein

A is S, $-CH=CH-$ or $-CH_2-CH_2-$;

A^2 is an aromatic or heteroaromatic divalent radical selected from para-phenylene, a 6-membered ring heteroaromatic divalent radical containing 1 or 2 ring nitrogens and a 5-membered ring heteroaromatic divalent radical containing one oxygen or sulfur ring atom and 0, 1 or 2 ring nitrogens in which heteroaromatic divalent radical the valences are in the 1,4- or 2,5- or 3,6- relationship and which divalent radical may bear a methyl, hydroxy or methoxy substituent (and more particularly, which divalent radical does not bear a substituent);

A^3 is an aromatic or heteroaromatic divalent radical selected from para-phenylene, a 6-membered ring heteroaromatic divalent radical containing 1 or 2 ring nitrogens and a 5-membered ring heteroaromatic divalent radical containing one oxygen or sulfur ring atom and 0, 1 or

2 ring nitrogens in which heteroaromatic divalent radical the valences are in the 1,4- or 2,5- or 3,6- relationship and which divalent radical may bear a (1-3C)alkyl, (1-2C)alkoxy or halo substituent (and more particularly, which divalent radical may bear a (1-3C)alkyl or halo substituent);

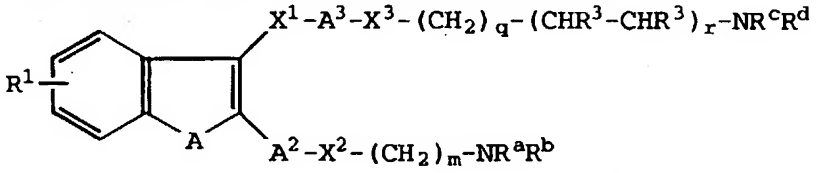
R^1 denotes 0, 1 or 2 substituents on the benz-ring independently selected from halo, methyl, ethyl, hydroxy, methoxy, carbamoyl, aminomethyl and hydroxymethyl;

X^1 is O, S, methylene, carbonyl or ethene-1,1-diyl;

X^2 is a direct bond, methylene, O or S; j and k are both 0; m is 1, 2, 3 or 4; provided that when m is 1, then X^2 is a direct bond; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is pyrrolidino, piperidino, morpholino or hexamethyleneimino;

X^3 is a direct bond, methylene, imino, O or S; q is 0, 1 or 2; and r is 0 or 1; provided that q and r are not both zero, and provided that when q is 1 and r is 0, then X^3 is a direct bond; each R^3 is hydrogen or the two R^3 groups together form a divalent radical $-(CH_2)_s-$ in which s is 3 or 4; and R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino, hexamethyleneimino or 1-imidazolyl.

A compound of formula I in which j and k are both 0 may be denoted as a compound of formula I'.



I'

A particular aspect of the above method is one wherein said compound is a compound of formula I in which

A is S, -CH=CH- or $-CH_2-CH_2-$;

A^2 is para-phenylene which may bear a substituent R^j ortho to the group X^2 and R^j is methyl, hydroxy or methoxy or A^2 is pyridine-2,5-diyl in which the 2-position is joined to X^2 (and more particularly, which divalent radical does not bear a substituent);

A^3 is para-phenylene which may bear a substituent R^e ortho to the group X^3 and R^e is (1-3)alkyl, (1-2C)alkoxy or halo or A^3 is pyridine-2,5-diyl in which the 2-position is joined to X^3 (and more particularly, R^e is (1-3)alkyl or halo);

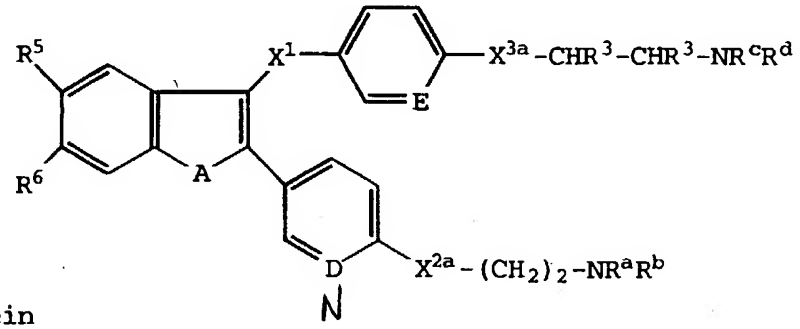
R^1 denotes 0, 1 or 2 substituents on the benz-ring independently selected from halo, methyl, ethyl, hydroxy, methoxy, carbamoyl, aminomethyl and hydroxymethyl;

X^1 is O, S, methylene, carbonyl or ethene-1,1-diyl;

X^2 is a direct bond, methylene, O or S; j and k are both 0; m is 1, 2, 3 or 4; provided that when m is 1, then X^2 is a direct bond; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is pyrrolidino, piperidino or morpholino;

X^3 is a direct bond, methylene, imino, O or S; q is 0, 1 or 2; and r is 0 or 1; provided that q and r are not both zero, and provided that when q is 1 and r is 0, then X^3 is a direct bond; each R^3 is hydrogen or the two R^3 groups together form a divalent radical $-(CH_2)_s-$ in which s is 3 or 4; and R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino, hexamethyleneimino or 1-imidazolyl.

A more particular aspect of any of the above methods is one wherein said compound is a compound of formula Ia



Ia

wherein

A is S, -CH=CH- or $-CH_2-CH_2-$;

D is CH, CR^j or N in which R^j is methyl, hydroxy or methoxy (and more particularly D is CH or N);

E is CH, CR^e or N in which R^e is (1-3C)alkyl, (1-2C)alkoxy or halo (and more particularly E is CH, CR^e or N in which R^e is (1-3C)alkyl or halo);

R^5 is hydrogen, halo, methyl, hydroxy or methoxy;

R^6 is hydrogen, hydroxy or methoxy;

X^1 is O, S, methylene, carbonyl or ethene-1,1-diyl;

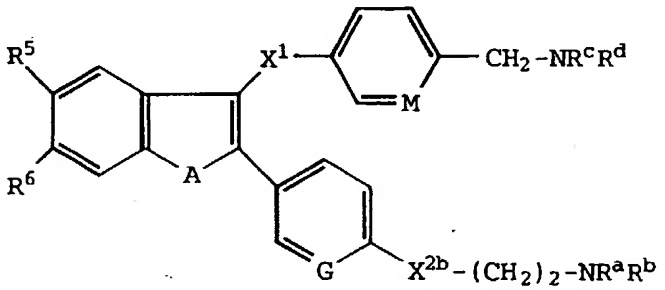
X^{2a} is methylene or O; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is pyrrolidino or piperidino;

X^{3a} is methylene, imino, O or S; and each R^3 is hydrogen or the two R^3 groups together form a divalent radical $-(CH_2)_s-$ in which s is 3 or 4; and R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino, hexamethyleneimino or 1-imidazolyl.

A particular method in which said compound is one of formula Ia is wherein A is S; D is CH; E is CR^e in which R^e is methoxy; R^5 is hydrogen; R^6 is hydroxy; X^1 is methylene; X^{2a} is O; and the group NR^aR^b is pyrrolidino; X^{3a} is O; and the two R^3 groups together form a divalent radical $-(CH_2)_s-$ in which s is 4 and which forms a trans-1,2-cyclohexanediyl group; and R^c and R^d are each methyl or the group NR^cR^d is pyrrolidino.

It will be clear that a compound of formula Ia also may be expressed as a compound of formula I or as a compound of formula I'.

An additional particular aspect of the above method is one wherein said compound of formula I is one which may be denoted as a compound of formula Ib



Ib

wherein

A is S, -CH=CH- or $-CH_2-CH_2-$;

G is CH, CR^k or N in which R^k is methyl, hydroxy or methoxy;

M is CH, CR^m or N in which R^m is (1-3C)alkyl, (1-2C)alkoxy or halo;

R^5 is hydrogen, halo, methyl, hydroxy or methoxy;

R^6 is hydrogen, hydroxy or methoxy;

X^1 is O, S, methylene, carbonyl or ethene-1,1-diyl;

X^{2b} is a direct bond or O; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is pyrrolidino or piperidino; and

R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is 2-(hydroxymethyl)-1-pyrrolidinyl, 2-(methoxymethyl)-1-pyrrolidinyl, pyrrolidino, piperidino or morpholino.

A more particular method in which said compound is one of formula Ib is wherein A is S; G is CH or N; M is CH, CR^m or N in which R^m is methyl, methoxy, chloro or bromo; R^5 is hydrogen; R^6 is hydroxy; X^1 is methylene; X^{2b} is a direct bond or O; the group NR^aR^b is pyrrolidino; and R^c and R^d are each methyl or the group NR^cR^d is 2-(hydroxymethyl)-1-pyrrolidinyl, 2-(methoxymethyl)-1-pyrrolidinyl, pyrrolidino or morpholino.

A further particular aspect of any of the above methods is one wherein said compound is one in which X^1 is methylene.

A further particular aspect of any of the above methods (in which the radical $-(CH_2)_s-$ is present) is one wherein said compound is one in which s is 4.

Another particular aspect of any of the above methods is one wherein said compound is one in which A is S.

A further particular aspect of any of the above methods is one wherein said compound is a compound of formula I in which R^1 denotes a hydroxy substituent at the position corresponding to the 6-position of a benzo[*b*]thiophene or a compound of formula Ia or of formula Ib in which R^5 is hydrogen and R^6 is hydroxy.

A selected aspect of the above methods is one in which said compound is a compound of formula Ia in which A is S, D is CH or N, E is CH or N, R^5 is hydrogen, R^6 is hydroxy, the group $-X^{2a}-(CH_2)_2-NR^aR^b$ is 2-(1-pyrrolidinyl)ethoxy, and the group $-X^{3a}-CHR^3-CHR^3-NR^cR^d$ is 3-(1-pyrrolidinyl)propyl 2-(1-pyrrolidinyl)ethoxy, trans-2-(1-pyrrolidinyl)cyclohexyloxy or trans-2-(1-piperidyl)cyclohexyloxy.

A preferred method of the invention includes one wherein said compound of formula I is one of those described herein at Examples 123, 124 and 164.

The present invention also provides a method of inhibiting coagulation in a mammal comprising administering to a mammal in need of treatment, a coagulation inhibiting dose of a thrombin inhibiting compound of formula I having any of the above definitions.

The present invention further provides a method of inhibiting thrombin comprising administering to a mammal in need of treatment, a thrombin inhibiting dose of a thrombin inhibiting compound of formula I having any of the above definitions.

Further, the present invention provides a method of treating a thromboembolic disorder comprising administering to a mammal in need of treatment, an effective dose of a thrombin inhibiting compound of formula I having any of the above definitions.

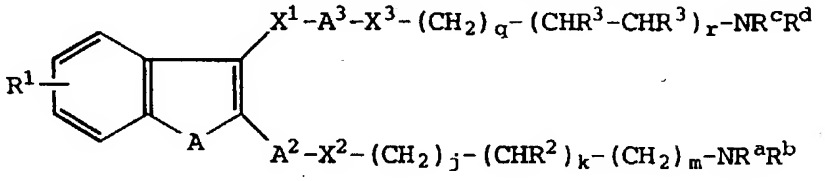
In addition, there is provided the use of a thrombin inhibiting compound of formula I having any of the above definitions for the manufacture of a medicament for treatment of a thromboembolic disorders.

As a further aspect of the invention, there is provided a prodrug (or a pharmaceutically acceptable salt thereof) of any of the above described thrombin inhibiting compounds of formula I which will form a prodrug. A compound of formula I (or formula Ia or formula Ib) which will form a prodrug includes one in which R^1 (or R^5 or R^6) or a substituent on A^2 or A^3 is hydroxy, carbamoyl, aminomethyl or hydroxymethyl, or one in which one or both of R^a and R^b is

hydrogen or the group NR^aR^b includes a hydroxymethyl group, or one in which R^2 is hydroxy, or one in which one or both of R^c and R^d is hydrogen or the group NR^cR^d includes a hydroxymethyl group. Particular compounds of formula I (or formula Ia) which will form a prodrug include those in which R^1 (or R^5 or R^6) is hydroxy, carbamoyl, aminomethyl or hydroxymethyl or in which one or both of R^a and R^b is hydrogen. (It will be recognized that a thrombin inhibiting compound of formula I also may serve as a prodrug for a different thrombin inhibiting compound of formula I).

As an additional feature of the invention there is provided a pharmaceutical formulation comprising in association with a pharmaceutically acceptable carrier, diluent or excipient, a prodrug of a thrombin inhibiting compound of formula I (or of a pharmaceutically acceptable salt thereof) as provided in any of the above descriptions.

Certain diamine compounds corresponding to formula I are included in the generic disclosure of United States Patent 4,133,814; issued to Jones et al., as antifertility agents. Weak antifertility activity is described therein for the compound 2-[4-(2-pyrrolidino-ethoxy)phenyl]-3-[4-(2-pyrrolidinoethoxy)benzoyl]-benzo[*b*]thiophene (isolated as its dicitrate salt). The remaining thrombin inhibiting compounds of formula I are believed to be novel and, thus, to constitute an additional aspect of the invention. Thus, according to the invention there is provided a novel compound of formula I (or a pharmaceutically acceptable salt thereof)



I

wherein

A is O, S, -CH=CH- or $-CH_2-CH_2-$;

A^2 is an aromatic or heteroaromatic divalent radical selected from para-phenylene, a 6-membered ring

heteroaromatic divalent radical containing 1 or 2 ring nitrogens in which the valences are in the 1,4- or 2,5- or 3,6- relationship, and a 5-membered ring heteroaromatic divalent radical containing one oxygen or sulfur ring atom and 0, 1 or 2 ring nitrogens in which the valences are in the 2,5- (or 3,5-) relationship and which divalent radical may bear a (1-3C)alkyl, (1-2C)alkoxy, hydroxy or halo substituent;

A^3 is an aromatic or heteroaromatic divalent radical selected from para-phenylene, a 6-membered ring heteroaromatic divalent radical containing 1 or 2 ring nitrogens in which the valences are in the 1,4- or 2,5- or 3,6- relationship, and a 5-membered ring heteroaromatic divalent radical containing one oxygen or sulfur ring atom and 0, 1 or 2 ring nitrogens in which the valences are in the 2,5- (or 3,5-) relationship and which divalent radical may bear one or two substituents independently selected from (1-4C)alkyl, halo, trifluoromethyl, (1-2C)alkoxy, hydroxy, cyano, aminomethyl, nitro, $-NHCH_2R^f$, $-NHC(O)R^f$ or $-NHS(O)_2R^g$ in which R^f is hydrogen or (1-2C)alkyl and R^g is (1-2C)alkyl or phenyl;

R^1 denotes 0, 1 or 2 substituents on the benz-ring independently selected from halo, methyl, ethyl, hydroxy, methoxy, carbamoyl, aminomethyl and hydroxymethyl;

X^1 is O, S, methylene, carbonyl or ethene-1,1-diyl;

(a) X^2 is imino, a direct bond, methylene, O or S; j is 0; k is 0; m is 1, 2, 3 or 4; provided that when m is 1, then X^2 is a direct bond; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is 2-(hydroxymethyl)-1-pyrrolidinyl, 2-(methoxymethyl)-1-pyrrolidinyl, pyrrolidino, piperidino, 2-methyl-1-piperidinyl, morpholino or hexamethyleneimino; or

(b) X^2 is imino, O or S; j is 1; k is 1; m is 1; R^2 is hydroxy; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is pyrrolidino, piperidino, morpholino or hexamethyleneimino; or

(c) X^2 is imino, O or S; j is 1; k is 1; m is 0; R^2 is hydroxymethyl or methoxycarbonyl; and R^a and R^b are independently hydrogen or (1-3C)alkyl; or

(d) X^2 is imino, O or S; j is 0, 1, 2 or 3; k is 1; m is 0 or 1; provided that j and m are not both 0; R^2 and R^a together form a diradical $-(CH_2)_n-$ in which n is 2, 3 or 4 and the sum of m and n is 3 or 4; and R^b is hydrogen or (1-3C)alkyl; or

(e) X^2 is -NH-C(O)-; j is 0; k is 0; m is 1; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is pyrrolidino, piperidino, morpholino or hexamethyleneimino; and

(1) X^3 is a direct bond, methylene, imino, O or S; q is 0, 1 or 2; and r is 0 or 1; provided that q and r are not both zero, and provided that when q is 1 and r is 0, then X^3 is a direct bond; each R^3 is hydrogen or the two R^3 groups together form a divalent radical $-(CH_2)_s-$ in which s is 3 or 4; and R^c and R^d are independently hydrogen or (1-4C)alkyl or the group NR^cR^d is 2-(hydroxymethyl)-1-pyrrolidinyl, 2-(methoxymethyl)-1-pyrrolidinyl, pyrrolidino, piperidino, morpholino, hexamethyleneimino, 1-imidazolyl or 4,5-dihydro-1-imidazolyl; or

(2) X^3 is imino, O or S; q is 0; r is 1; one R^3 group is (1-5C)alkyl and the other R^3 group is independently hydrogen or (1-5C)alkyl; and R^c and R^d are independently hydrogen or (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino or hexamethyleneimino; or

(3) X^3 is imino, O or S; q is 0, 1 or 2; r is 1; one R^3 group is hydrogen and the other R^3 group together with the group R^c forms a divalent radical $-(CH_2)_t-$ in which t is 2, 3 or 4 such that the resulting ring is a pyrrolidine or piperidine; and R^d is hydrogen or (1-3C)alkyl; or

(4) X^3 is $-N(R^h)-$; q is 0; r is 1; the R^3 group on the carbon bonded to X^3 and the group R^h together form a diradical $-(CH_2)_3-$; the other R^3 group is hydrogen; and R^c and

R^d are independently (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino or hexamethyleneimino; or

(5) X^3 is ethene-1,2-diyl or ethyne-1,2-diyl; q is 1; r is 0; and R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino or hexamethyleneimino;

provided that the compound is not one in which A is S; A^2 is para-phenylene; A^3 is para-phenylene; R^1 denotes zero substituents on the benz-ring or R^1 denotes a hydroxy or methoxy substituent at the 6-position of the benzo[*b*]thiophene ring; X^1 is carbonyl; X^2 is O; j and k are both 0, the group $-(CH_2)_m-$ is ethylene; R^a and R^b are independently (1-3C)alkyl or the group NR^aR^b is pyrrolidino, piperidino, morpholino or hexamethyleneimino; X^3 is O; the group $-(CH_2)_q-(CHR^3-CHR^3)_r-$ is ethylene; and R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino or hexamethyleneimino.

One particular novel compound of formula I, or a pharmaceutically acceptable salt thereof, is one wherein

A is S, -CH=CH- or $-CH_2-CH_2-$;

A^2 is an aromatic or heteroaromatic divalent radical selected from para-phenylene, a 6-membered ring heteroaromatic divalent radical containing 1 or 2 ring nitrogens and a 5-membered ring heteroaromatic divalent radical containing one oxygen or sulfur ring atom and 0, 1 or 2 ring nitrogens in which heteroaromatic divalent radical the valences are in the 1,4- or 2,5- or 3,6- relationship and which divalent radical may bear a methyl, hydroxy or methoxy substituent (and more particularly, which divalent radical does not bear a substituent);

A^3 is an aromatic or heteroaromatic divalent radical selected from para-phenylene, a 6-membered ring heteroaromatic divalent radical containing 1 or 2 ring nitrogens and a 5-membered ring heteroaromatic divalent radical containing one oxygen or sulfur ring atom and 0, 1 or 2 ring nitrogens in which heteroaromatic divalent radical the

valences are in the 1,4- or 2,5- or 3,6- relationship and which divalent radical may bear a (1-3C)alkyl, (1-2C)alkoxy or halo substituent (and more particularly, which divalent radical may bear a (1-3C)alkyl or halo substituent);

R^1 denotes 0, 1 or 2 substituents on the benz-ring independently selected from halo, methyl, ethyl, hydroxy, methoxy, carbamoyl, aminomethyl and hydroxymethyl;

X^1 is O, S, methylene, carbonyl or ethene-1,1-diyl;

X^2 is a direct bond, methylene, O or S; j and k are both 0; m is 1, 2, 3 or 4; provided that when m is 1, then X^2 is a direct bond; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is pyrrolidino, piperidino, morpholino or hexamethyleneimino;

X^3 is a direct bond, methylene, imino, O or S; q is 0, 1 or 2; and r is 0 or 1; provided that q and r are not both zero, and provided that when q is 1 and r is 0, then X^3 is a direct bond; each R^3 is hydrogen or the two R^3 groups together form a divalent radical $-(CH_2)_s-$ in which s is 3 or 4; and R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino, hexamethyleneimino or 1-imidazolyl.

A particular novel compound of formula I as described above is one in which

A is S, -CH=CH- or $-CH_2-CH_2-$;

A^2 is para-phenylene which may bear a substituent R^j ortho to the group X^2 and R^j is methyl, hydroxy or methoxy or A^2 is pyridine-2,5-diyl in which the 2-position is joined to X^2 (and more particularly, which divalent radical does not bear a substituent);

A^3 is para-phenylene which may bear a substituent R^e ortho to the group X^3 and R^e is (1-3)alkyl, (1-2C)alkoxy or halo or A^3 is pyridine-2,5-diyl in which the 2-position is joined to X^3 (and more particularly, R^e is (1-3)alkyl or halo);

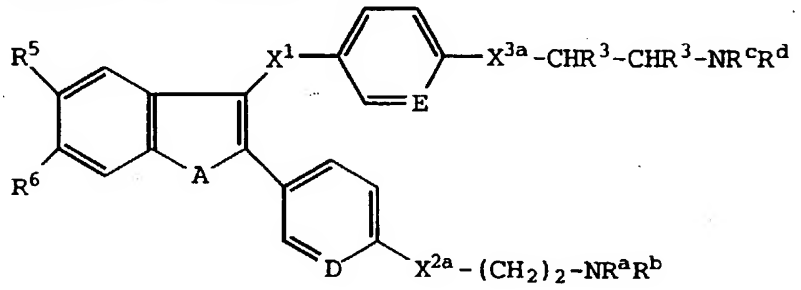
R^1 denotes 0, 1 or 2 substituents on the benz-ring independently selected from halo, methyl, ethyl, hydroxy, methoxy, carbamoyl, aminomethyl and hydroxymethyl;

X^1 is O, S, methylene, carbonyl or ethene-1,1-diyl;

X^2 is a direct bond, methylene, O or S; j and k are both 0; m is 1, 2, 3 or 4; provided that when m is 1, then X^2 is a direct bond; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is pyrrolidino, piperidino or morpholino;

X^3 is a direct bond, methylene, imino, O or S; q is 0, 1 or 2; and r is 0 or 1; provided that q and r are not both zero, and provided that when q is 1 and r is 0, then X^3 is a direct bond; each R^3 is hydrogen or the two R^3 groups together form a divalent radical $-(CH_2)_s-$ in which s is 3 or 4; and R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino, hexamethyleneimino or 1-imidazolyl.

A more particular novel compound of the invention is a compound of formula Ia



Ia

wherein

A is S, -CH=CH- or $-CH_2-CH_2-$;

D is CH, CR^j or N in which R^j is methyl, hydroxy or methoxy (and more particularly D is CH or N);

E is CH, CR^e or N in which R^e is (1-3C)alkyl, (1-2C)alkoxy or halo (and more particularly E is CH, CR^e or N in which R^e is (1-3C)alkyl or halo);

R^5 is hydrogen, halo, methyl, hydroxy or methoxy;

R^6 is hydrogen, hydroxy or methoxy;

X^1 is O, S, methylene, carbonyl or ethene-1,1-diyl;

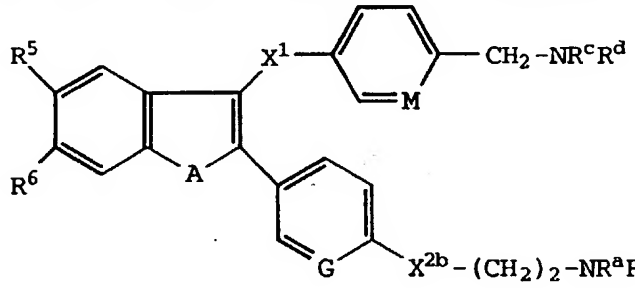
X^{2a} is methylene or O; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is pyrrolidino or piperidino;

X^{3a} is methylene, imino, O or S; and each R^3 is hydrogen or the two R^3 groups together form a divalent radical $-(CH_2)_s-$ in which s is 3 or 4; and R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino, hexamethyleneimino or 1-imidazolyl;

provided that the compound is not one in which A is S; D is CH; E is CH; R^5 is hydrogen, R^6 is hydrogen, hydroxy or methoxy; X^1 is carbonyl; X^{2a} is O; R^a and R^b are independently (1-3C)alkyl or the group NR^aR^b is pyrrolidino or piperidino; X^{3a} is O; each R^3 is hydrogen; and R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino or hexamethylenemino.

A particular novel compound of formula Ia is one wherein A is S; D is CH; E is CR^e in which R^e is methoxy; R^5 is hydrogen; R^6 is hydroxy; X^1 is methylene; X^{2a} is O; and the group NR^aR^b is pyrrolidino; X^{3a} is O; and the two R^3 groups together form a divalent radical $-(CH_2)_s-$ in which s is 4 and which forms a trans-1,2-cyclohexanediyl group; and R^c and R^d are each methyl or the group NR^cR^d is pyrrolidino.

An additional particular novel compound of formula I is one which may be denoted as a compound of formula Ib



Ib

wherein

A is S, -CH=CH- or $-CH_2-CH_2-$;

G is CH, CR^k or N in which R^k is methyl, hydroxy or methoxy;

M is CH, CR^m or N in which R^m is (1-3C)alkyl, (1-2C)alkoxy or halo;

R^5 is hydrogen, halo, methyl, hydroxy or methoxy;

R^6 is hydrogen, hydroxy or methoxy;

X^1 is O, S, methylene, carbonyl or ethene-1,1-diyl;

X^{2b} is a direct bond or O; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is pyrrolidino or piperidino; and

R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is 2-(hydroxymethyl)-1-pyrrolidinyl, 2-(methoxymethyl)-1-pyrrolidinyl, pyrrolidino, piperidino or morpholino.

A more particular novel compound is one of formula Ib is wherein A is S; G is CH or N; M is CH, CR^m or N in which R^m is methyl, methoxy, chloro or bromo; R^5 is hydrogen; R^6 is hydroxy; X^1 is methylene; X^{2b} is a direct bond or O; the group NR^aR^b is pyrrolidino; and R^c and R^d are each methyl or the group NR^cR^d is 2-(hydroxymethyl)-1-pyrrolidinyl, 2-(methoxymethyl)-1-pyrrolidinyl, pyrrolidino or morpholino.

A further particular novel compound of the invention is any of the above novel compounds wherein X^1 is methylene.

A further particular novel compound of the invention is any of the above novel compounds wherein s is 4.

Another particular novel compound of the invention is any of the above novel compounds wherein A is S.

A further particular novel compound of the invention is any of the above novel compounds wherein said compound is a compound of formula I in which R^1 denotes a hydroxy substituent at the position corresponding to the 6-position of a benzo[*b*]thiophene or a compound of formula Ia or of formula Ib in which R^5 is hydrogen and R^6 is hydroxy.

A selected novel compound of the above novel compounds is a compound of formula Ia in which A is S, D is CH or N, E is CH or N, R^5 is hydrogen, R^6 is hydroxy, the group $-X^{2a}-(CH_2)_2-NR^aR^b$ is 2-(1-pyrrolidinyl)ethoxy, and the group $-X^{3a}-CHR^3-CHR^3-NR^cR^d$ is 3-(1-pyrrolidinyl)propyl,

2-(1-pyrrolidinyl)ethoxy, trans-2-(1-pyrrolidinyl)-cyclohexyloxy or trans-2-(1-piperidyl)cyclohexyloxy.

A preferred novel compound of the invention includes one wherein said compound of formula I is one of those described herein at Examples 123, 124 and 164.

A pharmaceutically acceptable salt of an antithrombotic diamine of the instant invention includes one which is an acid-addition salt made with an acid which provides a pharmaceutically acceptable anion. Thus, an acid additon salt of a novel compound of formula I as provided above made with an acid which affords a pharmaceutically acceptable anion provides a particular aspect of the invention. Examples of such acids are provided hereinbelow.

As an additional aspect of the invention there is provided a pharmaceutical formulation comprising in association with a pharmaceutically acceptable carrier, diluent or excipient, a novel compound of formula I (or a pharmaceutically acceptable salt thereof) as provided in any of the above descriptions.

In this specification, the following definitions are used, unless otherwise described: Halo is fluoro, chloro, bromo or iodo. Alkyl, alkoxy, etc. denote both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain ("normal") radical, a branched chain isomer such as "isopropyl" being specifically denoted.

It will be appreciated that certain compounds of formula I (or salts or prodrugs, etc.) (such as when R^3 is not hydrogen) may exist in, and be isolated in, isomeric forms, including cis- or trans-isomers, as well as optically active, racemic, or diastereomeric forms. It is to be understood that the present invention encompasses a compound of formula I as a mixture of diastereomers, as well as in the form of an individual diastereomer, and that the present invention encompasses a compound of formula I as a mixture of enantiomers, as well as in the form of an individual enantiomer, any of which mixtures or form possesses

inhibitory properties against thrombin, it being well known in the art how to prepare or isolate particular forms and how to determine inhibitory properties against thrombin by standard tests including those described below.

In addition, a compound of formula I (or salt or prodrug, etc.) may exhibit polymorphism or may form a solvate with water or an organic solvent. The present invention also encompasses any such polymorphic form, any solvate or any mixture thereof.

Particular values are listed below for radicals, substituents, and ranges, for illustration only, and they do not exclude other defined values or other values within defined ranges for the radicals and substituents.

A particular value for a (1-2C)alkyl group is methyl or ethyl; for a (1-3C)alkyl group is methyl, ethyl, propyl or isopropyl; for a (1-4C)alkyl group is methyl, ethyl, propyl, isopropyl or butyl; for a (1-5C)alkyl group is methyl, ethyl, propyl, isopropyl, butyl or pentyl; and for a (1-2C)alkoxy group is methoxy or ethoxy.

A particular value for A^2 or A^3 when it is a 6-membered ring heteroaromatic divalent radical is pyridin-2,5-diyl, pyridazin-3,6-diyl, pyrazin-2,5-diyl, or pyrimidin-2,5-diyl (and more particularly, pyridin-2,5-diyl or pyrazin-2,5-diyl; especially pyridin-2,5-diyl). A particular value for A^2 or A^3 when it is a 5-membered ring heteroaromatic divalent radical is furan-2,5-diyl, thiophen-2,5-diyl, oxazol-2,5-diyl, thiazol-2,5-diyl, isoxazol-3,5-diyl, isothiazol-3,5-diyl, 1,3,4-oxadiazol-2,5-diyl or 1,3,4-thiadiazol-2,5-diyl (and more particularly, isoxazol-3,5-diyl).

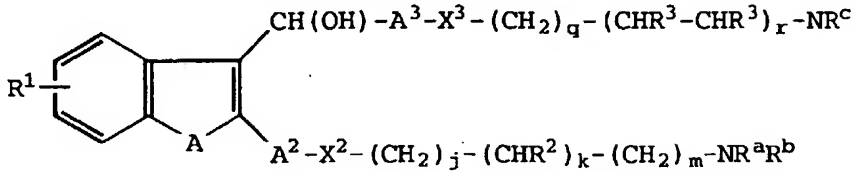
A compound of formula I may be made by processes which include processes known in the chemical art for the production of known compounds of formula I or of structurally analogous compounds or by a novel process described herein. A process for a novel compound of formula I (or a pharmaceutically acceptable salt thereof), novel processes for a compound of formula I and novel intermediates for the

manufacture of a compound of formula I as defined above provide further features of the invention and are illustrated by the following procedures in which the meanings of the generic radicals are as defined above, unless otherwise specified. It will be recognized that it may be preferred or necessary to prepare a compound of formula I in which a functional group is protected using a conventional protecting group, then to remove the protecting group to provide the compound of formula I.

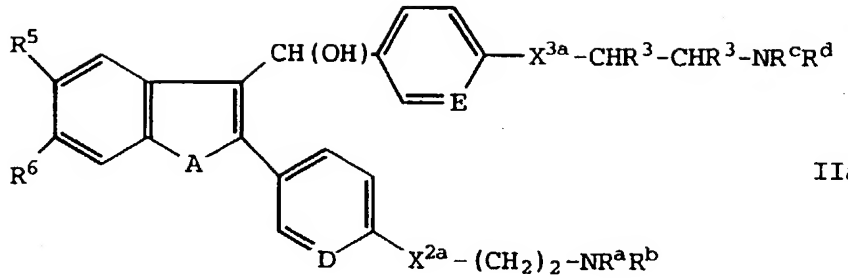
Thus, there is provided a process for preparing a novel compound of formula I (or a pharmaceutically acceptable salt thereof) as provided in any of the above descriptions which is selected from:

(A) For a compound of formula I in which X^1 is ethene-1,1-diyl, methylenation of a corresponding compound of formula I in which X^1 is carbonyl. The methylenation conveniently is carried out using methylidenetriphenylphosphorane generated *in situ* from methylidenetriphenylphosphonium bromide and a strong base such as potassium tert-butoxide in an inert solvent such as tetrahydrofuran in a manner similar to that described in Example 12, Part A, for the preparation of an intermediate compound.

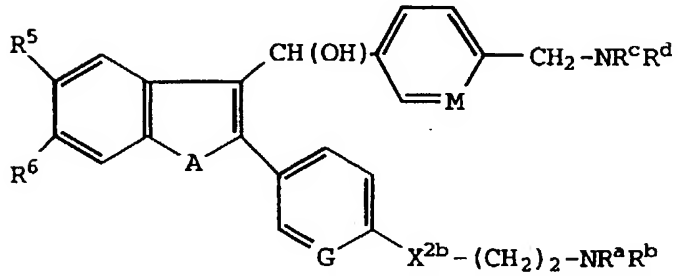
(B) For a compound of formula I (or formula Ia or formula Ib) in which X^1 is methylene, reductive removal of the hydroxy group of a corresponding alcohol of formula II (or formula IIa or formula IIb).



II



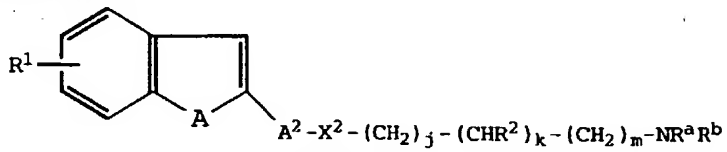
IIa



IIb

The reductive removal conveniently is carried out using sodium borohydride in trifluoroacetic acid in a manner similar to that described in Example 2, Part D, or using triethylsilane in trifluroracetic acid in a manner similar to that described in Example 3, Part E. An intermediate alcohol of formula II (or formula IIa or formula IIb) provides an additional feature of the invention; it may be obtained by reducing the carbonyl group of a corresponding ketone of formula I (or formula Ia or formula Ib) in which X^1 is carbonyl, for example by using lithium aluminium hydride in tetrahydrofuran in a manner similar to that described in Example 2, Part D, or Example 3, Part E or by using diisobutylaluminium hydride in tetrahydrofuran in a manner similar to that described in Example 32, Part A.

(C) For a compound of formula I in which A is O or S and X^1 is carbonyl, acylation of a corresponding compound of formula III



III

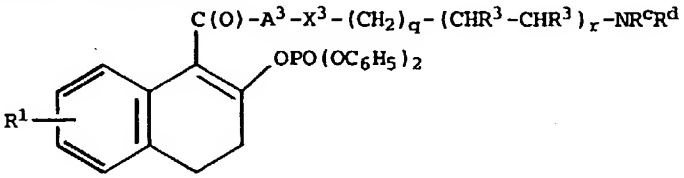
with an activated derivative of a corresponding acid of formula IV.

$$HOOC\text{-}A^3\text{-}X^3\text{-}(CH_2)_q\text{-}(CHR^3\text{-}CHR^3)_r\text{-}NR^cR^d \qquad IV$$

Conveniently, the acylation is carried out using the hydrochloride salt of the acid chloride of the acid formula IV and a catalyst such as aluminium chloride in a manner similar to that described in Example 1, Part C or titanium tetrachloride in a manner similar to that described in Example 2, Part C.

(D) For a compound of formula I in which A is -CH=CH-, selective dehydrogenation of a corresponding compound in which A is $-CH_2-CH_2-$, for example using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at 50 °C to 100 °C in an inert solvent such as dioxane.

(E) For a compound of formula I in which A is $-CH_2-CH_2-$ and X^2 is carbonyl, condensation of a corresponding compound of formula V



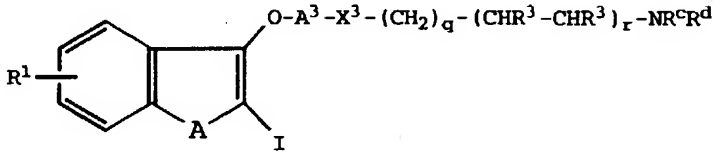
V

with a corresponding reagent of formula VI;

$$Br\text{-}Mg\text{-}A^2\text{-}X^2\text{-}(CH_2)_j\text{-}(CHR^2)_k\text{-}(CH_2)_m\text{-}NR^aR^b \qquad VI$$

for example, in an inert solvent such as tetrahydrofuran at about 0 °C.

(F) For a compound of formula I in which X^1 is O, cross coupling a corresponding compound of formula VII



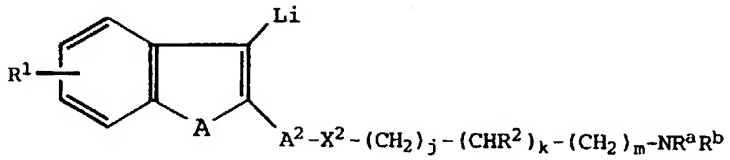
VII

with a corresponding boronic acid of formula VIII;

$$(HO)_2B\text{-}A^2\text{-}X^2\text{-}(CH_2)_j\text{-}(CHR^2)_k\text{-}(CH_2)_m\text{-}NR^aR^b \qquad VIII$$

for example, using a similar procedure to that described in Example 11, Part D for the preparation of an intermediate compound in which A is S.

(G) For a compound of formula I in which X^1 is O or S, treatment of a corresponding organolithium compound of formula IX



IX

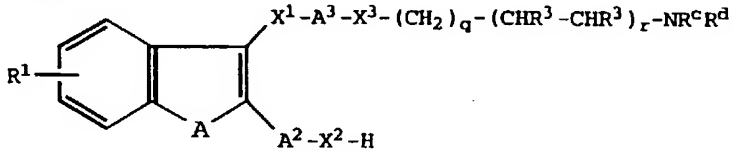
with a corresponding disulfide of formula X;

$$(-S-A^3-X^3-(CH_2)_q-(CHR^3-CHR^3)_r-NR^cR^d)_2 \qquad X$$

for example, using a similar procedure to that described in Example 10, Part B for the preparation of an intermediate compound in which A is S.

(H) For a compound of formula I in which R^1 or a substituent on A^2 or A^3 is hydroxy, removal of the O-methyl group of a corresponding compound of formula I in which R^1 or a substituent on A^2 or A^3 is methoxy. The removal may be carried out by any conventional manner consistent with the structure of the compound of formula I, for example, using aluminium chloride and ethanethiol in an inert solvent as described in Example 1, Part D.

(I) For a compound of formula I in which X^2 is O or S, alkylation at X^2 of a corresponding compound of formula XI



XI

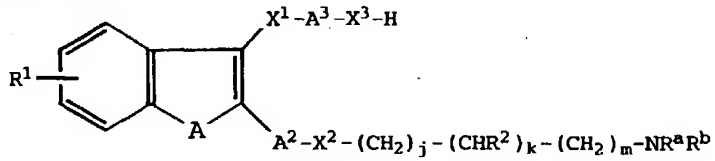
in which X^2 is O or S with a corresponding compound of formula XII

$$L-(CH_2)_j-(CHR^2)_k-(CH_2)_m-NR^aR^b \qquad XII$$

in which L denotes a leaving group. It may be preferred to generate the leaving group of the compound of formula XII *in situ* from the corresponding hydroxy compound and perform the

alkylation under Mitsunobu conditions using triphenylphosphine and diethyl azodicarboxylate in an inert solvent, for example, as described in Example 4, Part B for the preparation of an intermediate compound. Alternatively, a compound of formula XII in which L is chloro, bromo, iodo or a sulfonate, such as methanesulfonate or p-toluenesulfonate, may be used, preferably in conjunction with a base such as cesium carbonate, using a similar procedure to that described in Example 3, Part D, for example as described in Example 5, Part C.

(J) For a compound of formula I in which X^3 is O or S, alkylation at X^3 of a corresponding compound of formula XIII



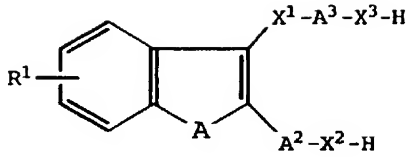
XIII

in which X^3 is O or S with a corresponding compound of formula XIV

$$L\text{-}(CH_2)_q\text{-}(CHR^3\text{-}CHR^3)_r\text{-}NR^cR^d \qquad \text{XIV}$$

in which L denotes a leaving group as defined above. It may be preferred to generate the leaving group of the compound of formula XIV from the corresponding hydroxy compound and to perform the alkylation under Mitsunobu conditions as described above. Alternatively, L may have any of the values described above for L, and the alkylation may be carried out using a similar procedure to that described in Example 3, Part D.

(K) For a compound of formula I in which X^2 and X^3 are O or S and in which $-(CH_2)_j\text{-}(CHR^2)_k\text{-}(CH_2)_m\text{-}NR^aR^b$ is the same as $-(CH_2)_q\text{-}(CHR^3\text{-}CHR^3)_r\text{-}NR^cR^b$, dialkylation of a compound of formula XV



XV

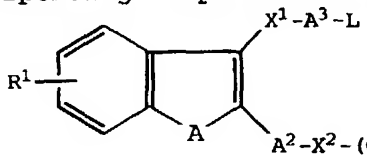
with a compound of formula XII. The dialkylation may be carried out as described above for the alkylation of a compound of formula XI or formula XIII, for example as described in Example 8, Part D or Example 10, Part D.

(L) For a compound of formula I in which R^1 is carbamoyl, aminolysis of a corresponding intermediate compound of formula I in which R^1 is a lower alkoxy-carbonyl group, such as a methoxy-carbonyl group. The aminolysis is conveniently carried out using anhydrous ammonia in a lower alcohol under pressure, for example, as described in Example 30, Part E.

(M) For a compound of formula I in which R^1 or a substituent on A^3 or the value of $-X^3-(CH_2)_q-(CHR^3-CHR^3)_r-NR^cR^b$ is aminomethyl, reduction of an intermediate compound corresponding to a compound of formula I but in which R^1 is cyano or of a corresponding compound of formula I in which a substituent on A^3 is cyano or of an intermediate compound corresponding to a compound of formula I but in which $-X^3-(CH_2)_q-(CHR^3-CHR^3)_r-NR^cR^b$ is cyano. The reduction conveniently is carried out using lithium aluminium hydride in tetrahydrofuran, for example as described in Example 31, Part D for the preparation of an intermediate alcohol of formula II in which R^1 is aminomethyl or as described in Example 162.

(N) For a compound of formula I in which R^1 or R^2 is hydroxymethyl, reduction of a corresponding intermediate compound of formula I in which R^1 or R^2 is a lower alkoxy-carbonyl group, such as a methoxy-carbonyl group. The reduction is conveniently carried out using diisobutyl-aluminium hydride in toluene and tetrahydrofuran, for example, as described in Example 32, Part A for the preparation of an intermediate alcohol of formula II in which R^1 is hydroxymethyl or as described in Example 168.

(O) For a compound of formula I in which A^3 is pyridine-2,5-diyl in which the 2-position is joined to X^3 and X^3 is O, displacement of the leaving group L of a corresponding compound of formula XVI,



XVI

in which L is defined as above, with an alkali metal alkoxide of an alcohol of formula XVII,

$$HO-(CH_2)_q-(CHR^3-CHR^3)_r-NR^cR^d \qquad XVII$$

for example with the sodium alkoxide. The reaction is conveniently carried out with a compound of formula XVI in which L is chloro and the sodium alkoxide derived from an alcohol of formula XVII using conditions described in Example 9, Part B and further illustrated in Example 33, Part B.

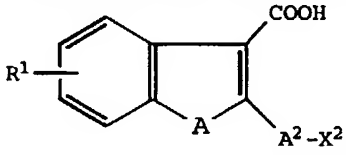
(P) For a compound of formula I in which A^3 bears a (1-4C)alkyl substituent, substitution of the bromo group of a corresponding compound of formula I in which A^3 bears a bromo substituent. The substitution is conveniently carried out using a tetralkyltin reagent and a palladium(0) catalyst in an inert solvent, for example as described in Example 8, Part B for the preparation of an intermediate compound.

(Q) For a compound of formula I in which X^1 is carbonyl, condensation of a corresponding organolithium compound of formula IX with a derivative of a corresponding acid of formula IV which will provide a ketone upon condensation. Derivatives of an acid of formula IV which will provide a ketone upon condensation include the lithium salt of the acid, corresponding amides such as the N-methoxy-N-methyl amide, and the corresponding nitrile. The condensation is typically carried out in an inert, aprotic solvent, for example tetrahydrofuran, at or below ambient temperature.

(R) For a compound of formula I in which X^1 is carbonyl, condensation of a corresponding organolithium compound of formula XVIII

$$Li\text{-}A^3\text{-}X^3\text{-}(CH_2)_q\text{-}(CHR^3\text{-}CHR^3)_r\text{-}NR^cR^d \qquad \text{XVIII}$$

with a derivative of a corresponding acid of formula XIX

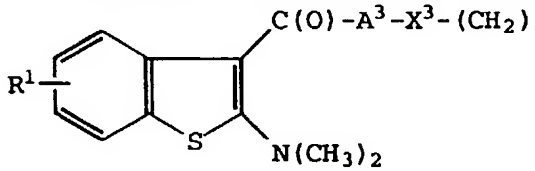


XIX

which will provide a ketone upon condensation. Derivatives of an acid of formula XIX which will provide a ketone upon condensation include the lithium salt of the acid, corresponding amides such as the N-methoxy-N-methyl amide, and the corresponding nitrile. The reaction is typically carried out as described above in procedure (Q).

(S) For a compound of formula I in which A is -CH=CH- and X^1 is methylene, elimination of water from a corresponding compound of formula II in which A is $-CH_2-CH_2-$. The elimination conveniently is effected using an acid catalyst, for example by heating the compound of formula II in a solution of anhydrous ethanolic HCl.

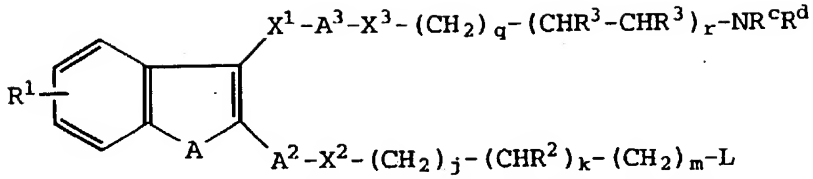
(T) For a compound of formula I in which A is S and X^1 is carbonyl, condensation of a compound of formula XXV



XXV

with a corresponding reagent of formula VI. The condensation conveniently is carried out in an inert solvent such as tetrahydrofuran at about 0 °C, for example as described in Example 34, Part B.

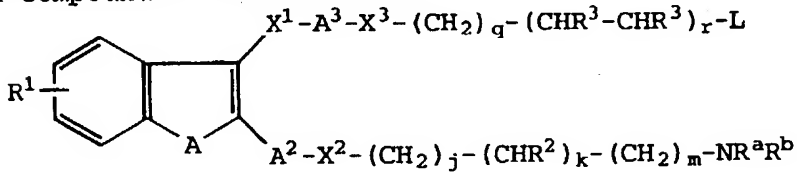
(U) Alkylation of an amine of formula HNR^aR^b with a compound of formula XXVI



XXVI

wherein L is a leaving group as defined above, or for a compound of formula I in which R^2 is OH, wherein L and R^2 form an epoxide. Conveniently, the alkylation is carried out by heating the reagents in a polar solvent, for example as described in Example 43, Part C or in Example 116, Part B.

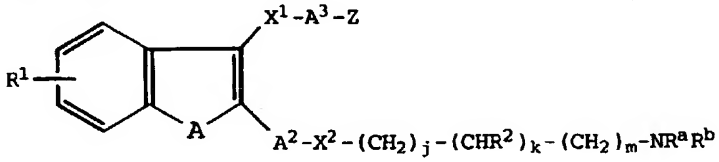
(V) Alkylation of an amine of formula HNR^cR^d with a compound of formula XXVII



XXVII

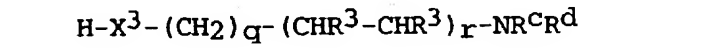
wherein L is a leaving group as defined above. Conveniently, the alkylation is carried out by mixing the reagents in a polar solvent, for example as described in Example 129, Part C.

(W) For a compound of formula I in which X^1 is carbonyl (particularly wherein A^3 is unsubstituted or substituted para-phenylene) and X^3 is imino, O, S or $-N(R^h)-$, substitution of the group Z wherein Z is fluoro or nitro (particularly wherein Z is fluoro) of a ketone of formula XXVIII



XXVIII

using a compound of formula XXIX,



XXIX

or a metal salt thereof, preferably an alkali metal salt. Conveniently, the substitution reaction is carried out by heating the reagents XXVIII and XXIX in dimethylformamide or tetrahydrofuran using sodium hydride or potassium carbonate,

for example as illustrated in Example 59, Part B; in Example 121, Part B; in Example 145, Part C; in Example 147 or in Example 117, Part D for the preparation of an intermediate of formula XXV.

(X) For a compound of formula I in which a substituent on A^3 is amino, reduction of a corresponding compound of formula I in which a substituent on A^3 is nitro. The reduction may be carried out using a conventional method, for example by catalytic hydrogenation as described in Example 97.

(Y) For a compound of formula I in which a substituent on A^3 is $-NHC(O)R^f$ or $-NHS(O)_2R^g$, substitution of the amino group of a corresponding compound of formula I in which a substituent on A^3 is amino using an activated derivative of an acid of formula $HOC(O)R^f$ or $HOS(O)_2R^g$. Conveniently, the activated derivative is the acid anhydride or the acid chloride, and the substitution is carried out in a polar solvent, for example as in Example 111 or Example 113.

(Z) For a compound of formula I in which a substituent on A^3 is $-NHCH_2R^f$ or a compound of formula I in which $-(CH_2)_j-(CHR^2)_k-(CH_2)_m-NR^aR^b$ terminates in $-CH_2-NR^aR^b$, reduction of the amide of a corresponding compound of formula I in which a substituent on A^3 is $-NHC(O)R^f$ or of an intermediate compound corresponding to a compound of formula I but in which $-(CH_2)_j-(CHR^2)_k-(CH_2)_m-NR^aR^b$ terminates in $-C(O)NR^aR^b$. The reduction conveniently is carried out using lithium aluminum hydride in tetrahydrofuran, for example as described in Example 112 or Example 166, Part E.

(AA) For a compound of formula I in which X^3 is ethene-1,2-diyl, reduction of the triple bond of a corresponding compound of formula I in which X^3 is ethyne-1,2-diyl. For a compound of formula I in which the double bond is trans-, the reduction conveniently is effected using diisobutylaluminum hydride as described in Example 130; for a compound of formula I in which the double bond is cis-, the reduction conveniently is effected using hydrogenation over a Lindlar catalyst as described in Example 131.

(AB) For a compound of formula I in which a substituent on A^3 is cyano, substitution of the halo group of a corresponding compound of formula I in which a substituent on A^3 is bromo or iodo. The substitution conveniently is effected by heating the compound with cuprous cyanide in a polar solvent such as 1-methyl-2-pyrrolidinone as described in Example 161, Part A.

Whereafter, for any of the above procedures, when a functional group is protected using a protecting group, removing the protecting group.

Whereafter, for any of the above procedures, when a pharmaceutically acceptable salt of a compound of formula I is required, it may be obtained by reacting the basic form of such a compound of formula I with an acid affording a physiologically acceptable counterion or by any other conventional procedure.

A particular process of the invention is one selected from procedures (A)-(R) above for a novel compound of formula I wherein

A is S, -CH=CH- or $-CH_2-CH_2-$;

A^2 is an aromatic or heteroaromatic divalent radical selected from para-phenylene, a 6-membered ring heteroaromatic divalent radical containing 1 or 2 ring nitrogens and a 5-membered ring heteroaromatic divalent radical containing one oxygen or sulfur ring atom and 0, 1 or 2 ring nitrogens in which heteroaromatic divalent radical the valences are in the 1,4- or 2,5- or 3,6- relationship;

A^3 is an aromatic or heteroaromatic divalent radical selected from para-phenylene, a 6-membered ring heteroaromatic divalent radical containing 1 or 2 ring nitrogens and a 5-membered ring heteroaromatic divalent radical containing one oxygen or sulfur ring atom and 0, 1 or 2 ring nitrogens in which heteroaromatic divalent radical the valences are in the 1,4- or 2,5- or 3,6- relationship and which divalent radical may bear a (1-3C)alkyl or halo substituent;

R^1 denotes 0, 1 or 2 substituents on the benz-ring independently selected from halo, methyl, ethyl, hydroxy, methoxy, carbamoyl, aminomethyl and hydroxymethyl;

X^1 is O, S, methylene, carbonyl or ethene-1,1-diyl;

X^2 is a direct bond, methylene, O or S; j and k are both 0; m is 1, 2, 3 or 4; provided that when m is 1, then X^2 is a direct bond; and R^a and R^b are independently hydrogen or (1-3C)alkyl or the group NR^aR^b is pyrrolidino, piperidino, morpholino or hexamethyleneimino;

X^3 is a direct bond, methylene, imino, O or S; q is 0, 1 or 2; and r is 0 or 1; provided that q and r are not both zero, and provided that when q is 1 and r is 0, then X^3 is a direct bond; each R^3 is hydrogen or the two R^3 groups together form a divalent radical $-(CH_2)_s-$ in which s is 3 or 4; and R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino, hexamethyleneimino or 1-imidazolyl;

provided that the compound is not one in which A is S; A^2 is para-phenylene; A^3 is para-phenylene; R^1 denotes zero substituents on the benz-ring or R^1 denotes a hydroxy or methoxy substituent at the 6-position of the benzo[*b*]thiophene ring; X^1 is carbonyl; X^2 is O; the group $-(CH_2)_m-$ is ethylene; R^a and R^b are independently (1-3C)alkyl or the group NR^aR^b is pyrrolidino, piperidino, morpholino or hexamethyleneimino; X^3 is O; the group $-(CH_2)_q-(CHR^3-CHR^3)_r-$ is ethylene; and R^c and R^d are independently (1-3C)alkyl or the group NR^cR^d is pyrrolidino, piperidino, morpholino or hexamethyleneimino

whereafter, for any of the procedures (A)-(R), when a pharmaceutically acceptable salt of a compound of formula I is required, it is obtained by reacting the basic form of such a compound of formula I with an acid affording a physiologically acceptable counterion or by any other conventional procedure.

As mentioned above, a compound corresponding to a compound of formula I but in which a functional group is

protected may serve as an intermediate for a compound of formula I. Accordingly, such protected intermediates for a novel compound of formula I provide further aspects of the invention. Thus, as one particular aspect of the invention, there is provided a compound corresponding to a novel compound of formula I as defined above and bearing at least one substiutent R^1 which is hydroxy, but in which the corresponding substituent is $-OR^P$ in place of hydroxy, wherein R^P is a phenol protecting group other than methyl. Phenol protecting groups are well known in the art, for example as described in T.W. Greene and P.G.M. Wuts, "Protecting Groups in Organic Synthesis" (1991). Particular values of R^P include, for example, benzyl (for example as described in Example 41 or Example 81) and allyl (for example as described in Example 88). Further, R^P may denote a functionalized resin, for example as disclosed in H.V. Meyers, et al., Molecular Diversity, (1995), 1, 13-20.

As mentioned above, the invention includes pharmaceutically acceptable salts of the thrombin inhibiting compounds defined by the above formula I. A particular diamine of this invention possesses one or more sufficiently basic functional groups to react with any of a number of inorganic and organic acids affording a physiologically acceptable counterion to form a pharmaceutically acceptable salt. Acids commonly employed to form pharmaceutically acceptable acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluene sulfonic, methanesulfonic acid, oxalic acid, p-bromo phenyl sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts thus are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate,

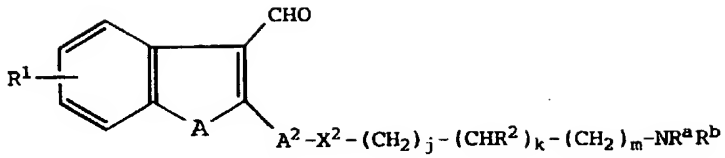
propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycollate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like. Preferred pharmaceutically acceptable acid addition salts include those formed with mineral acids such as hydrochloric acid, hydrobromic acid and sulfuric acid.

If not commercially available, the necessary starting materials for the preparation of a compound of formula I may be prepared by procedures which are selected from standard techniques of organic chemistry, including aromatic and heteroaromatic substitution and transformation, from techniques which are analogous to the syntheses of known, structurally similar compounds, and techniques which are analogous to the above described procedures or procedures described in the Examples. It will be clear to one skilled in the art that a variety of sequences is available for the preparation of the starting materials. Starting materials which are novel provide another aspect of the invention.

As noted above in procedure (B), an intermediate alcohol of formula II may be obtained by reduction of a corresponding ketone of formula I. In addition, an alcohol of formula II may be obtained by condensation of an organolithium compound of formula IX with a corresponding aldehyde of formula XX

$$H\text{-}C(O)\text{-}A^3\text{-}X^3\text{-}(CH_2)_q\text{-}(CHR^3\text{-}CHR^3)_r\text{-}NR^cR^d \qquad XX$$

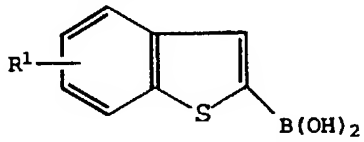
using a procedure similar to that described in procedure (Q) or by condensing an organolithium compound of formula XVIII with a corresponding aldehyde of formula XXI



XXI

using a procedure similar to that described in procedure (R), particularly when j and k are both 0.

An intermediate of formula III may be prepared by any of a number of known procedures. A preferred method for a compound of formula III in which A is S, particularly when j and k are both 0, is the cross coupling of a boronic acid of formula XXII



XXII

with a reagent of formula XXIII

$$X\text{-}A^2\text{-}X^2\text{-}(CH_2)_j\text{-}(CHR^2)_k\text{-}(CH_2)_m\text{-}NR^aR^b \qquad \text{XXIII}$$

in which X is, for example, bromo, iodo or trifluoromethanesulfonate, for example as described in Examples 1, 2, 4 and 16. For preparation of a compound of formula III in which A is O, a preferred method is a copper mediated cross coupling of a compound of formula XXIII and a 2-metalated benzofuran, such as described in Example 119, Part A. It may be preferred to cross couple a species in which the side chain is not fully elaborated, then to complete the elaboration, for example as described in Example 14 and in Example 119.

Starting material acids of formula IV may be prepared by a number of standard procedures, a number of which are described in the Examples.

Starting material enol phosphates of formula V may be prepared and used by methods similar to those described in Jones et al., J. Med. Chem. (1992), 35(5), 931-938; and the corresponding reagents of formula VI may be obtained by conventional methods from bromides of formula XXIII in which X is bromo.

A starting material iodide of formula VII in which A is S may be prepared in a manner similar to that described in Example 11, parts A and B, and the boronic acid of formula VIII may be obtained from a compound of formula XXIII using a procedure similar to that of Example 11, part C.

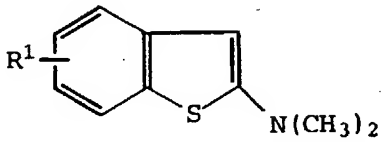
An organolithium compound of formula IX may be prepared by transmetallation of the corresponding bromide, which itself may be obtained by bromination of the compound corresponding to formula IX, but with hydrogen in the place of lithium. For a compound in which A is S, the procedure may be carried out in a manner similar to that described in Example 10, parts A and B.

A starting material of formula XI in which X^2 is O or S may be obtained by deprotection of X^2 of a corresponding compound in which X^2 bears a protecting group. When X^2 is O, it may be protected as a silyl ether, as described in Example 29, or as a methyl ether as described in several of the examples and cleaved by a variety of methods including by using pyridine hydrochloride (Example 5), aluminum chloride and ethanethiol (Examples 9, 13, 15, 17, 18, 24, 26 and 28, part C), or boron tribromide (see below).

A starting material of formula XIII in which X^3 is O or S may be obtained by deprotection of X^3 of a corresponding compound in which X^3 bears a protecting group. For example, when X^3 is O, it may be protected as a methyl ether and liberated by treatment with sodium thioethoxide (Example 28, part A), aluminum chloride and ethanethiol, or pyridine hydrochloride, depending upon the groups present in other parts of the molecule.

A starting material of formula XV in which X^2 and X^3 are O or S may be obtained by deprotection of X^2 and X^3 of a corresponding compound in which X^2 and X^3 bear protecting groups. For example, when X^2 and X^3 are both O, they may both be protected as methyl ethers and simultaneously deprotected by treatment with aluminum chloride and ethanethiol (Example 3) with boron tribromide (Examples 8 and 10) or with pyridine hydrochloride (Examples 11 and 12).

A starting material compound of formula XXV typically is prepared by acylation of a compound of formula XXIV



XXIV

with an activated derivative of an acid of formula VI, conveniently the acid chloride, for example as described in Example 39, Part B.

Selective methods of protection and deprotection are well known in the art for preparation of compounds such as those of formula XI, XIII and XV discussed above. Selective methods for cleavage of methyl ethers, as described in the examples, are discussed in Jones, et al., J. Med. Chem., (1984), 27, 1057-1066. For example, the diether 3-(4-methoxybenzoyl)-2-(4-methoxyphenyl)benzo[*b*]thiophene described at Example 3, part B, may be treated with boron tribromide in dichloromethane at -10 °C (1 hour) to afford the monoether 2-(4-hydroxyphenyl)-3-(4-methoxybenzoyl)benzo[*b*]thiophene, whereas treatment with sodium thioethoxide (Example 28, part A) affords the isomeric monoether 3-(4-hydroxybenzoyl)-2-(4-methoxyphenyl)benzo[*b*]-thiophene. Treatment with boron tribromide under less mild conditions (0°, 6 hours, see Example 8, part C) or with aluminum chloride and ethanethiol cleaves both ethers (Example 3, part C).

The compounds of the invention are isolated best in the form of acid addition salts. Salts of the compounds of formula I formed with acids such as those mentioned above are useful as pharmaceutically acceptable salts for administration of the antithrombotic agents and for preparation of formulations of these agents. Other acid addition salts may be prepared and used in the isolation and purification of the compounds.

As noted above, the optically active isomers and diastereomers of the compounds of formula I are also considered part of this invention. Such optically active

isomers may be prepared from their respective optically active precursors by the procedures described above, or by resolving the racemic mixtures. This resolution can be carried out by derivatization with a chiral reagent followed by chromatography or by repeated crystallization. Removal of the chiral auxiliary by standard methods affords substantially optically pure isomers of the compounds of the present invention or their precursors. Further details regarding resolutions can be obtained in Jacques, et al., Enantiomers, Racemates, and Resolutions, John Wiley & Sons, 1981.

The compounds of the invention are believed to selectively inhibit thrombin over other proteinases and nonenzyme proteins involved in blood coagulation without appreciable interference with the body's natural clot lysing ability (the compounds have a low inhibitory effect on fibrinolysis). Further, such selectivity is believed to permit use with thrombolytic agents without substantial interference with thrombolysis and fibrinolysis.

The invention in one of its aspects provides a method of inhibiting thrombin in mammals comprising administering to a mammal in need of treatment an effective (thrombin inhibiting) dose of a compound of formula I.

In another of its aspects, the invention provides a method of treating a thromboembolic disorder comprising administering to a mammal in need of treatment an effective (thromboembolic disorder therapeutic and/or prophylactic amount) dose of a compound of formula I.

The invention in another of its aspects provides a method of inhibiting coagulation in mammals comprising administering to a mammal in need of treatment an effective (coagulation inhibiting) dose of a compound of formula I.

The thrombin inhibition, coagulation inhibition and thromboembolic disorder treatment contemplated by the present method includes both medical therapeutic and/or prophylactic treatment as appropriate.

In a further embodiment the invention relates to treatment, in a human or animal, of conditions where inhibition of thrombin is required. The compounds of the invention are expected to be useful in animals, including man, in treatment or prophylaxis of thrombosis and hypercoagulability in blood and tissues. Disorders in which the compounds have a potential utility are in treatment or prophylaxis of thrombosis and hypercoagulability in blood and tissues. Disorders in which the compounds have a potential utility, in treatment and/or prophylaxis, include venous thrombosis and pulmonary embolism, arterial thrombosis, such as in myocardial ischemia, myocardial infarction, unstable angina, thrombosis-based stroke and peripheral arterial thrombosis. Further, the compounds have expected utility in the treatment or prophylaxis of atherosclerotic disorders (diseases) such as coronary arterial disease, cerebral arterial disease and peripheral arterial disease. Further, the compounds are expected to be useful together with thrombolytics in myocardial infarction. Further, the compounds have expected utility in prophylaxis for reocclusion after thrombolysis, percutaneous transluminal angioplasty (PTCA) and coronary bypass operations. Further, the compounds have expected utility in prevention of rethrombosis after microsurgery. Further, the compounds are expected to be useful in anticoagulant treatment in connection with artificial organs and cardiac valves. Further, the compounds have expected utility in anticoagulant treatment in hemodialysis and disseminated intravascular coagulation. A further expected utility is in rinsing of catheters and mechanical devices used in patients *in vivo*, and as an anticoagulant for preservation of blood, plasma and other blood products *in vitro*. Still further, the compounds have expected utility in other diseases where blood coagulation could be a fundamental contributing process or a source of secondary pathology, such as cancer, including metastasis, inflammatory diseases, including arthritis, and diabetes. The anti-coagulant compound is administered orally

or parenterally, e.g. by intravenous infusion (iv), intramuscular injection (im) or subcutaneously (sc).

The specific dose of a compound administered according to this invention to obtain therapeutic and/or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the compound administered, the rate of administration, the route of administration, and the condition being treated.

A typical daily dose for each of the above utilities is between about 0.01 mg/kg and about 1000 mg/kg. The dose regimen may vary e.g. for prophylactic use a single daily dose may be administered or multiple doses such as 3 or 5 times daily may be appropriate. In critical care situations a compound of the invention is administered by iv infusion at a rate between about 0.01 mg/kg/h and about 20 mg/kg/h and preferably between about 0.1 mg/kg/h and about 5 mg/kg/h.

The method of this invention also is practiced in conjunction with a clot lysing agent e.g. tissue plasminogen activator (t-PA), modified t-PA, streptokinase or urokinase. In cases when clot formation has occurred and an artery or vein is blocked, either partially or totally, a clot lysing agent is usually employed. A compound of the invention can be administered prior to or along with the lysing agent or subsequent to its use, and preferably further is administered along with aspirin to prevent the reoccurrence of clot formation.

The method of this invention is also practiced in conjunction with a platelet glycoprotein receptor (IIb/IIIa) antagonist, that inhibits platelet aggregation. A compound of the invention can be administered prior to or along with the IIb/IIIa antagonist or subsequent to its use to prevent the occurrence or reoccurrence of clot formation.

The method of this invention is also practiced in conjunction with aspirin. A compound of the invention can be administered prior to or along with aspirin or subsequent to

its use to prevent the occurrence or reoccurrence of clot formation. As stated above, preferably a compound of the present invention is administered in conjunction with a clot lysing agent and aspirin.

This invention also provides pharmaceutical formulations for use in the above described therapeutic method. Pharmaceutical formulations of the invention comprise an effective thrombin inhibiting amount of a compound of formula I in association with a pharmaceutically acceptable carrier, excipient or diluent. For oral administration the antithrombotic compound is formulated in gelatin capsules or tablets which may contain excipients such as binders, lubricants, disintegration agents and the like. For parenteral administration the antithrombotic is formulated in a pharmaceutically acceptable diluent e.g. physiological saline (0.9 percent), 5 percent dextrose, Ringer's solution and the like.

The compound of the present invention can be formulated in unit dosage formulations comprising a dose between about 0.1 mg and about 1000 mg. Preferably the compound is in the form of a pharmaceutically acceptable salt such as for example the sulfate salt, acetate salt or a phosphate salt. An example of a unit dosage formulation comprises 5 mg of a compound of the present invention as a pharmaceutically acceptable salt in a 10 ml sterile glass ampoule. Another example of a unit dosage formulation comprises about 10 mg of a compound of the present invention as a pharmaceutically acceptable salt in 20 ml of isotonic saline contained in a sterile ampoule.

The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. The compounds of the present invention are preferably formulated prior to administration. Another embodiment of the present invention is a pharmaceutical formulation comprising an effective amount of a novel compound of formula I or a pharmaceutically acceptable salt or solvate thereof in association with a

pharmaceutically acceptable carrier, diluent or excipient therefor.

The active ingredient in such formulations comprises from 0.1 percent to 99.9 percent by weight of the formulation. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The present pharmaceutical formulations are prepared by known procedures using well known and readily available ingredients. The compositions of this invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art. In making the compositions of the present invention, the active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, (as a solid or in a liquid medium), soft and hard gelatin capsules, suppositories, sterile injectable solutions, sterile packaged powders, and the like.

The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way. "Active ingredient," of course, means a compound according to Formula I or a pharmaceutically acceptable salt or solvate thereof.

Formulation 1: Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2: A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Active ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 3: An aerosol solution is prepared containing the following components:

	Weight
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	70.00
Total	100.00

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30 °C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4: Tablets, each containing 60 mg of active ingredient, are made as follows:

Active ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10 % solution in water)	4 mg

Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50 °C and passed through a No. 18 mesh U.S. Sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5: Capsules, each containing 80 mg of active ingredient, are made as follows:

Active ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6: Suppositories, each containing 225 mg of active ingredient, are made as follows:

Active ingredient	225 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7: Suspensions, each containing 50 mg of active ingredient per 5 ml dose, are made as follows:

Active ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8: An intravenous formulation may be prepared as follows:

Active ingredient	100 mg
Isotonic saline	1,000 ml

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

The ability of the compounds of the present invention to be an effective and orally active thrombin inhibitor are evaluated in one or more of the following assays.

The compounds provided by the invention (formula I) selectively inhibit the action of thrombin in mammals. The inhibition of thrombin is demonstrated by *in vitro* inhibition of the amidase activity of thrombin as measured in an assay in which thrombin hydrolyzes the chromogenic substrate, N-benzoyl-L-phenylalanyl-L-valyl-L-arginyl-p-nitroanilide, N-benzoyl-L-Phe-L-Val-L-Arg-p-nitroanilide.

The assay is carried out by mixing 50 µl buffer (0.03M Tris, 0.15M NaCl, pH 7.4) with 25 µl of human thrombin solution (purified human thrombin, Enzyme Research Laboratories, South Bend, Indiana, at 8 NIH units/ml) and 25

µl of test compound in a solvent (50% aqueous methanol (v:v)). Then 150 µl of an aqueous solution of the chromogenic substate (at 0.25 mg/ml) are added and the rates of hydrolysis of the substrate are measured by monitoring the reactions at 405 nm for the release of p-nitroaniline. Standard curves are constructed by plotting free thrombin concentration against hydrolysis rate. The hydrolysis rates observed with test compounds are then converted to "free thrombin" values in the respective assays by use of the standard curves. The bound thrombin (bound to test compound) is calculated by subtracting the amount of free thrombin observed in each assay from the known initial amount of thrombin used in the assay. The amount of free inhibitor in each assay is calculated by subtracting the number of moles of bound thrombin from the number of moles of added inhibitor (test compound).

The Kass value is the hypothetical equilibrium constant for the reaction between thrombin and the test compound (I).

$$\text{Thrombin} + \text{I} \rightleftharpoons \text{Thrombin-I}$$

$$\text{Kass} = \frac{[\text{Thrombin-I}]}{[(\text{Thrombin}) \times (\text{I})]}$$

Kass is calculated for a range of concentrations of test compounds and the mean value reported in units of liter per mole. In general, a thrombin inhibiting compound of formula I of the instant insertion exhibits a Kass of 0.03×10^6 L/mole or much greater. For example, the compound of Example 3 was found to have a Kass of 5.0×10^6 L/mole, and the compound of Example 164 was found to have a Kass of 526×10^6 L/mole.

By substantially following the procedures described above for human thrombin, and using other human blood coagulation system serine proteases and using fibrinolytic system serine proteases, with the appropriate chromogenic substrates, identified below, the selectivity of the compounds of the present invention with respect to the coagulation factor serine proteases and to the fibronolytic

serine proteases are evaluated as well as their substantial lack of interference with human plasma clot fibrinolysis.

Human factors X, Xa, IXa, XIa, and XIIa are purchased from Enzyme Research Laboratories, South Bend, Indiana; human urokinase from Leo Pharmaceuticals, Denmark; and recombinant activated Protein C (aPC) is prepared at Eli Lilly and Co. substantially according to U.S. Patent 4,981,952. Chromogenic substrates: N-Benzoyl-Ile-Glu-Gly-Arg-p-nitroanilide (for factor Xa); N-Cbz-D-Arg-Gly-Arg-p-nitroanilide (for factor IXa assay as the factor Xa substrate); Pyroglutamyl-Pro-Arg-p-nitroanilide (for Factor XIa and for aPC); H-D-Pro-Phe-Arg-p-nitroanilide (for factor XIIa); and Pyroglutamyl-Gly-Arg-p-nitroanilide (for urokinase); are purchased from Kabi Vitrum, Stockholm, Sweden, or from Midwest Biotech, Fishers, Indiana. Bovine trypsin is purchased from Worthington Biochemicals, Freehold, New Jersey, and human plasma kallikrein from Kabi Vitrum, Stockholm, Sweden. Chromogenic substrate H-D-Pro-Phe-Arg-p-nitroanilide for plasma kallikrein is purchased from Kabi Vitrum, Stockholm, Sweden. N-Benzoyl-Phe-Val-Arg-p-nitroanilide, the substrate for human thrombin and for trypsin, is synthesized according to procedures described above for the compounds of the present invention, using known methods of peptide coupling from commercially available reactants, or purchased from Midwest Biotech, Fishers, Indiana.

Human plasmin is purchased from Boehringer Mannheim, Indianapolis, Indiana; nt-PA is purchased as single chain activity reference from American Diagnostica, Greenwich, Connecticut; modified-t-PA6 (mt-PA6) is prepared at Eli Lilly and Company by procedure known in the art (See, Burck, et al., J. Biol. Chem., 265, 5120-5177 (1990). Plasmin chromogenic substrate H-D-Val-Leu-Lys-p-nitroanilide and tissue plasminogen activator (t-PA) substrate H-D-Ile-Pro-Arg-p-nitroanilide are purchased from Kabi Vitrum, Stockholm, Sweden.

In the chromogenic substrates described above the three-letter symbols Ile, Glu, Gly, Pro, Arg, Phe, Val, Leu and Lys are used to indicate the corresponding amino acid group isoleucine, glutamic acid, glycine, proline, arginine, phenylalanine, valine, leucine and lysine, respectively.

Thrombin inhibitors preferably should spare fibrinolysis induced by urokinase, tissue plasminogen activator (t-PA) and steptokinase. This would be important to the therapeutic use of such agents as an adjunct to streptokinase, t-PA or urokinase thrombolytic therapy and to the use of such agents as an endogenous fibrinolysis-sparing (with respect to t-PA and urokinase) antithrombotic agents. In addition to the lack of interference with the amidase activity of the fibrinolytic proteases, such fibrinolytic system sparing can be studied by the use of human plasma clots and their lysis by the respective fibrinolytic plasminogen activators.

Materials

Dog plasma is obtained from conscious mixed-breed hounds (either sex Hazelton-LRE, Kalamazoo, Michigan, U.S.A.) by venipuncture into 3.8 percent citrate. Fibrinogen is prepared from fresh dog plasma and human fibrinogen is prepared from in-date ACD human blood at the fraction I-2 according to previous procedures and specifications. Smith, Biochem. J., 185, 1-11 (1980); and Smith, et al., Biochemistry, 11, 2958-2967, (1972). Human fibrinogen (98 percent pure/plasmin free) is from American Diagnostica, Greenwich, Connecticut. Radiolabeling of fibrinogen I-2 preparations is performed as previously reported. Smith, et al., Biochemistry, 11, 2958-2967, (1972). Urokinase is purchased from Leo Pharmaceuticals, Denmark, as 2200 Ploug units/vial. Streptokinase is purchased from Hoechst-Roussel Pharmaceuticals, Somerville, New Jersey.

Methods - Effects on Lysis of Human Plasma Clots by t-PA

Human plasma clots are formed in micro test tubes by adding 50 µL thrombin (73 NIH unit/mL) to 100 µL human plasma which contains 0.0229 µCi 125-iodine labeled fibrinogen. Clot lysis is studied by overlaying the clots with 50 µL of urokinase or streptokinase (50, 100, or 1000 unit/mL) and incubating for 20 hours at room temperature. After incubation the tubes are centrifuged in a Beckman Microfuge. 25 µL of supernate is added into 1.0 mL volume of 0.03 M tris/0.15 M NaCl buffer for gamma counting. Counting controls 100 percent lysis are obtained by omitting thrombin (and substituting buffer). The thrombin inhibitors are evaluated for possible interference with fibrinolysis by including the compounds in the overlay solutions at 1, 5, and 10 µg/mL concentrations. Rough approximations of IC_{50} values are estimated by linear extrapolations from data points to a value which would represent 50 percent of lysis for that particular concentration of fibrinolytic agent.

Anticoagulant Activity

Materials

Dog plasma and rat plasma are obtained from conscious mixed-breed hounds (either sex, hazelton-LRE, Kalamazoo, Michigan, U.S.A.) or from anesthetized male Sprague-Dawley rats (Harlan Sprague-Dawley, Inc., Indianapolis, Indiana, U.S.A.) by venipuncture into 3.8 percent citrate. Fibrinogen is prepared from in-date ACD human blood as the fraction I-2 according to previous procedures and specifications. Smith, Biochem. J., 185, 1-11 (1980); and Smith, et al., Biochemistry, 11, 2958-2967 (1972). Human fibrinogen is also purchased as 98 percent pure/plasmin free from American Diagnostica, Greenwich, Connecticut. Coagulation reagents Actin, Thromboplastin, Innovin and Human plasma are from Baxter Healthcare Corp., Dade Division, Miami, Florida. Bovine thrombin from Parke-Davis (Detroit, Michigan) is used for coagulation assays in plasma.

Methods

Anticoagulation Determinations

Coagulation assay procedures are as previously described. Smith, et al., Thrombosis Research, 50, 163-174 (1988). A CoAScreener coagulation instrument (American LABor, Inc.) is used for all coagulation assay measurements. The prothrombin time (PT) is measured by adding 0.05 mL saline and 0.05 mL Thromboplastin-C reagent or recombinant human tissue factor reagent (Innovin) to 0.05 mL test plasma. The activated partial thromboplastin time (APTT) is measured by incubation of 0.05 mL test plasma with 0.05 mL Actin reagent for 120 seconds followed by 0.05 mL $CaCl_2$ (0.02 M). The thrombin time (TT) is measured by adding 0.05 mL saline and 0.05 mL thrombin (10 NIH units/mL) to 0.05 mL test plasma. The compounds of formula I are added to human or animal plasma over a wide range of concentrations to determine prolongation effects on the APTT, PT, and TT assays. Linear extrapolations are performed to estimate the concentrations required to double the clotting time for each assay. For preferred compounds of the instant invention, a concentration of 30 ng/mL or less typically is sufficient to double the TT.

Animals

Male Sprague Dawley rats (350-425 gm, Harlan Sprague Dawley Inc., Indianapolis, IN) are anesthetized with xylazine (20 mg/kg, s.c.) and ketamine (120 mg/kg, s.c.) and maintained on a heated water blanket (37 °C). The jugular vein(s) is cannulated to allow for infusions.

Arterio-Venous shunt model

The left jugular vein and right carotid artery are cannulated with 20 cm lengths of polyethylene PE 60 tubing. A 6 cm center section of larger tubing (PE 190) with a cotton thread (5 cm) in the lumen, is friction fitted between the longer sections to complete the arterio-venous shunt circuit. Blood is circulated through the shunt for 15 min before the thread is carefully removed and weighed. The weight of a wet thread

is subtracted from the total weight of the thread and thrombus (see J.R. Smith, Br J Pharmacol, 77:29, 1982). In this model preferred compounds of the instant invention reduce the net clot weight to approximately 25-30% of control, or even lower, at an i.v. dose of 33.176 µmol/kg/h.

$FeCl_3$ model of arterial injury

The carotid arteries are isolated via a midline ventral cervical incision. A thermocouple is placed under each artery and vessel temperature is recorded continuously on a strip chart recorder. A cuff of tubing (0.058 ID x 0.077 OD x 4 mm, Baxter Med. Grade Silicone), cut longitudinally, is placed around each carotid directly above the thermocouple. $FeCl_3$ hexahydrate is dissolved in water and the concentration (20 percent) is expressed in terms of the actual weight of $FeCl_3$ only. To injure the artery and induce thrombosis, 2.85 µL is pipetted into the cuff to bathe the artery above the thermocouple probe. Arterial occlusion is indicated by a rapid drop in temperature. The time to occlusion is reported in minutes and represents the elapsed time between application of $FeCl_3$ and the rapid drop in vessel temperature (see K.D. Kurz, Thromb. Res., 60:269, 1990).

Spontaneous thrombolysis model

In vitro data suggests that thrombin inhibitors inhibit thrombin and, at higher concentrations, may inhibit other serine proteases, such as plasmin and tissue plasminogen activator. To assess if the compounds inhibit fibrinolysis *in vivo*, the rate of spontaneous thrombolysis is determined by implanting a labeled whole blood clot into the pulmonary circulation. Rat blood (1 mL) is mixed rapidly with bovine thrombin (4 IU, Parke Davis) and ^{125}I human Fibrogen (5 µCi, ICN), immediately drawn into silastic tubing and incubated at 37 °C for 1 hour. The aged thrombus is expelled from the tubing, cut into 1 cm segments, washed 3X in normal saline and each segment is counted in a gamma counter. A segment with known counts is aspirated into a catheter that is

subsequently implanted into the jugular vein. The catheter tip is advanced to the vicinity of the right atrium and the clot is expelled to float into the pulmonary circulation. One hour after implant, the heart and lungs are harvested and counted separately. Thrombolysis is expressed as a percentage where:

$$\% \text{ Thrombolysis} = \frac{(\text{injected cpm} - \text{lung cpm})}{\text{injected cpm}} \times 100$$

The fibrinolytic dissolution of the implanted clot occurs time-dependently (see J.P. Clozel, Cardiovas. Pharmacol., 12:520, 1988).

Coagulation parameters

Plasma thrombin time (TT) and activated partial thromboplastin time (APTT) are measured with a fibrometer. Blood is sampled from a jugular catheter and collected in syringe containing sodium citrate (3.8 percent, 1 part to 9 parts blood). To measure TT, rat plasma (0.1 mL) is mixed with saline (0.1 mL) and bovine thrombin (0.1 mL, 30 U/mL in TRIS buffer; Parke Davis) at 37 °C. For APTT, plasma (0.1 mL) and APTT solution (0.1 mL, Organon Teknika) are incubated for 5 minutes (37 °C) and $CaCl_2$ (0.1 mL, 0.025 M) is added to start coagulation. Assays are done in duplicate and averaged.

Index of Bioavailability

For a measure of bioactivity, plasma thrombin time (TT) serves as a substitute for the assay of parent compound on the assumption that observed increments in TT resulted from thrombin inhibition by parent only. The time course of the effect of the thrombin inhibitor upon TT is determined after i.v bolus administration to anesthetized rats and after oral treatment of fasted conscious rats. Due to limitations of blood volume and the number of points required to determine the time course from time of treatment to the time when the response returns to pretreatment values, two populations of rats are used. Each sample population represents alternating

sequential time points. The average TT over the time course is used to calculate area under the curve (AUC). The index of bioavailability is calculated by the formula shown below and is expressed as percent relative activity.

The area under the curve (AUC) of the plasma TT time course is determined and adjusted for the dose. This index of bioavailability is termed "% Relative Activity" and is calculated as

$$\%\text{Relative Activity} = \frac{\text{AUC po}}{\text{AUC iv}} \times \frac{\text{Dose iv}}{\text{Dose po}} \times 100$$

Compounds

Compound solutions are prepared fresh daily in normal saline and are injected as a bolus or are infused starting 15 minutes before and continuing throughout the experimental perturbation which is 15 minutes in the arteriovenous shunt model and 60 minutes in the $FeCl_3$ model of arterial injury and in the spontaneous thrombolysis model. Bolus injection volume is 1 mL/kg for i.v., and 5 mL/kg for p.o., and infusion volume is 3 mL/hr.

Statistics

Results are expressed as means +/- SEM. One-way analysis of variance is used to detect statistically significant differences and then Dunnett's test is applied to determine which means are different. Significance level for rejection of the null hypothesis of equal means is $P<0.05$.

Animals

Male dogs (Beagles; 18 months - 2 years; 12-13 kg, Marshall Farms, North Rose, New York 14516) are fasted overnight and fed Purina certified Prescription Diet (Purina Mills, St. Louis, Missouri) 240 minutes after dosing. Water is available *ad libitum*. The room temperature is maintained between 66-74 °F; 45-50 percent relative humidity; and lighted from 0600-1800 hours.

Pharmacokinetic model.

Test compound is formulated immediately prior to dosing by dissolving in sterile 0.9 percent saline to a 5 mg/mL preparation. Dogs are given a single 2 mg/kg dose of test compound by oral gavage. Blood samples (4.5 mL) are taken from the cephalic vein at 0.25, 0.5, 0.75, 1, 2, 3, 4 and 6 hours after dosing. Samples are collected in citrated Vacutainer tubes and kept on ice prior to reduction to plasma by centrifugation. Plasma samples are analyzed by HPLC MS. Plasma concentration of test compound is recorded and used to calculate the pharmacokinetic parameters: elimination rate constant, Ke; total clearance, Clt; volume of distribution, V_D; time of maximum plasma test compound concentration, Tmax; maximum concentration of test compound of Tmax, Cmax; plasma half-life, $t_{0.5}$; and area under the curve, A.U.C.; fraction of test compound absorbed, F.

Canine Model of Coronary Artery Thrombosis

Surgical preparation and instrumentation of the dogs are as described in Jackson, et al., Circulation, 82, 930-940 (1990). Mixed-breed hounds (aged 6-7 months, either sex, Hazelton-LRE, Kalamazoo, MI, U.S.A.) are anesthetized with sodium pentobarbital (30 mg/kg intravenously, i.v.), intubated, and ventilated with room air. Tidal volume and respiratory rates are adjusted to maintain blood PO_2, PCO_2, and pH within normal limits. Subdermal needle electrodes are inserted for the recording of a lead II ECG.

The left jugular vein and common carotid artery are isolated through a left mediolateral neck incision. Arterial blood pressure (ABP) is measured continuously with a precalibrated Millar transducer (model (MPC-500, Millar Instruments, Houston, TX, U.S.A.) inserted into the carotid artery. The jugular vein is cannulated for blood sampling during the experiment. In addition, the femoral veins of both hindlegs are cannulated for administration of test compound.

A left thoracotomy is performed at the fifth intercostal space, and the heart is suspended in a pericardial cradle. A 1- to 2-cm segment of the left circumflex coronary artery (LCX) is isolated proximal to the first major diagonal ventricular branch. A 26-gauge needle-tipped wire anodal electrode (Teflon-coated, 30-gauge silverplated copper wire) 3-4 mm long is inserted into the LCX and placed in contact with the intimal surface of the artery (confirmed at the end of the experiment). The stimulating circuit is completed by placing the cathode in a subcutaneous (s.c.) site. An adjustable plastic occluder is placed around the LCX, over the region of the electrode. A precalibrated electromagnetic flow probe (Carolina Medical Electronics, King, NC, U.S.A.) is placed around the LCX proximal to the anode for measurement of coronary blood flow (CBF). The occluder is adjusted to produce a 40-50 percent inhibition of the hyperemic blood flow response observed after 10-s mechanical occlusion of the LCX. All hemodynamic and ECG measurements are recorded and analyzed with a data acquisition system (model M3000, Modular Instruments, Malvern, PA. U.S.A.).

Thrombus Formation and Compound Administration Regimens

Electrolytic injury of the intima of the LCX is produced by applying 100-μA direct current (DC) to the anode. The current is maintained for 60 min and then discontinued whether the vessel has occluded or not. Thrombus formation proceeds spontaneously until the LCX is totally occluded (determined as zero CBF and an increase in the S-T segment). Compound administration is started after the occluding thrombus is allowed to age for 1 hour. A 2-hour infusion of the compounds of the present invention at doses of 0.5 and 1 mg/kg/hour is begun simultaneously with an infusion of thrombolytic agent (e.g. tissue plasminogen activator, streptokinase, APSAC). Reperfusion is followed for 3 hour after administration of test compound. Reocclusion of coronary arteries after successful thrombolysis is defined as zero CBF which persisted for ≥ 30 minutes.

Hematology and template bleeding time determinations

Whole blood cell counts, hemoglobin, and hematocrit values are determined on a 40-µl sample of citrated (3.8 percent) blood (1 part citrate:9 parts blood) with a hematology analyzer (Cell-Dyn 900, Sequoia-Turner. Mount View, CA, U.S.A.). Gingival template bleeding times are determined with a Simplate II bleeding time device (Organon Teknika Durham, N.C., U.S.A.). The device is used to make 2 horizontal incisions in the gingiva of either the upper or lower left jaw of the dog. Each incision is 3 mm wide x 2 mm deep. The incisions are made, and a stopwatch is used to determine how long bleeding occurs. A cotton swab is used to soak up the blood as it oozes from the incision. Template bleeding time is the time from incision to stoppage of bleeding. Bleeding times are taken just before administration of test compound (0 min), 60 min into infusion, at conclusion of administration of the test compound (120 min), and at the end of the experiment.

All data are analyzed by one-way analysis of variance (ANOVA) followed by Student-Neuman-Kuels post hoc *t* test to determine the level of significance. Repeated-measures ANOVA are used to determine significant differences between time points during the experiments. Values are determined to be statistically different at least at the level of $p<0.05$. All values are mean ± SEM. All studies are conducted in accordance with the guiding principles of the American Physiological Society. Further details regarding the procedures are described in Jackson, et al., J. Cardiovasc. Pharmacol., (1993), 21, 587-599.

The following Examples are provided to further describe the invention and are not to be construed as limitations thereof.

The abbreviations, symbols and terms used in the examples have the following meanings.

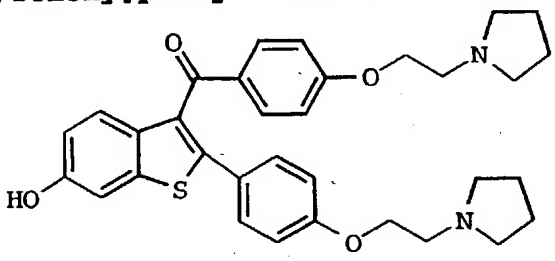
Ac = acetyl
AIBN = azobisisobutyronitrile
Anal. = elemental analysis
Bu = butyl
n-BuLi = butyllithium
calcd = calculated
DIBAL-H = diisobutyl aluminum hydride
DMF = dimethylformamide
DMSO = dimethylsulfoxide
Et = ethyl
EtOAc = ethyl acetate
Et_3N = triethylamine
Et_2O = diethyl ether
EtOH = ethanol
EtSH = ethanethiol
FAB = Fast Atom Bombardment (Mass Spectrascopy)
FDMS = field desorption mass spectrum
Hex = hexanes
HPLC = High Performance Liquid Chromatography
HRMS = high resolution mass spectrum
i-PrOH = isopropanol
IR = Infrared Spectrum
LAH = lithium aluminum hydride
Me = methyl
MeI = methyl iodide
MeOH = methanol
MPLC = Medium Pressure Liquid Chromatography
NBS = N-bromosuccinimide
NMR = Nuclear Magnetic Resonance
Ph = phenyl
PPA = polyphosphoric acid
i-Pr = isopropyl
Rochelle's Salt = potassium sodium tartrate
RPHPLC = Reversed Phase High Performance Liquid Chromatography
SiO_2 = silica gel
SM = starting material

TEA = triethylamine
Temp. = temperature
TFA = trifluoroacetic acid
THF = tetrahydrofuran
TIPS = triisopropylsilyl
TLC = thin layer chromatography
triflic acid = trifluoromethanesulfonic acid

Unless otherwise stated, pH adjustments and work up are with aqueous acid or base solutions. PrepLC indicates preparative liquid chromatography using "Prep Pak (TM)" silica cartridges; radial chromatography indicates preparative chromatography using a "Chromatotron (TM)" instrument.

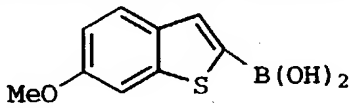
Example 1

Preparation of 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

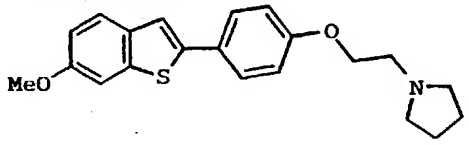
Part A. 6-Methoxybenzo[*b*]thiophene-2-boronic Acid.



To a solution of 6-methoxybenzo[*b*]thiophene (Graham, S. L., et al. *J. Med. Chem.* **1989**, *32*, 2548-2554)(18.13 g, 0.111 mol) in 150 mL of anhydrous THF at -60 °C was added *n*-BuLi (76.2 mL, 0.122 mol, 1.6 M solution in hexanes), dropwise via syringe. After stirring for 30 min, triisopropyl borate (28.2 mL, 0.122 mol) was introduced via syringe. The resulting mixture was allowed to gradually warm to 0 °C and then partitioned between 1.0 N HCl and EtOAc (300 mL each). The layers were separated, and the organic phase was dried over Na_2SO_4. Concentration *in vacuo* produced a white solid that was triturated from Et_2O/hexanes. Filtration provided 16.4 g (71%) of 6-methoxybenzo[*b*]thiophene-2-boronic acid as a white solid.

mp 200 °C (dec); FDMS 208 (M^+; 100); ^1H NMR (DMSO-d_6) δ 8.36 (br s), 7.86-7.75 (m, 2H), 7.53 (dd, *J* = 8.1 and 2.0 Hz, 1H), 6.98 (m, 1H), 3.82 (s, 3H).

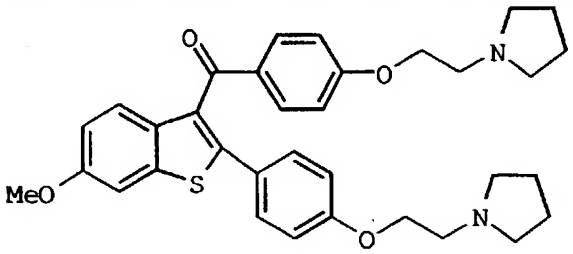
Part B. 6-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene.



To a slurry of 6-methoxybenzo[*b*]thiophene-2-boronic acid (Example 1, Part A) (6.43 g, 30.9 mmol) in 310 mL of benzene was added 1-(2-(4-bromophenoxy)ethyl)pyrrolidine (5.80 mL, 28.1 mmol). Upon addition the reaction mixture turned to a yellow homogeneous solution. The reaction flask was then covered with aluminum foil to keep out light. To this was added 1.07 g (0.92 mmol) of tetrakis(triphenylphosphine)-palladium(0), followed by 30 mL of 2.0 N sodium carbonate solution. The biphasic mixture was heated at 85 °C for 3 h with vigorous stirring. The mixture was cooled to 0 °C and 175 mL of brine solution was added. The layers were separated and the aqueous layer was extracted with 1.0 L of EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by PrepLC (53:35:2 THF-hexanes-TEA) to afford 5.42 g (15.3 mmol, 55%) of an off-white solid.

mp 151-154 °C; ^1H NMR ($CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 2H), 7.33 (s, 1H), 7.29 (d, *J* = 2.3 Hz, 1H), 6.95 (d, *J* = 8.7 Hz, 3H), 4.18 (t, *J* = 5.9 Hz, 2H), 3.88 (s, 3H), 2.97 (t, *J* = 5.9 Hz, 2H), 2.71 (br t, 4H), 1.85 (m, 4H); FDMS: 353 (M^+); Anal. Calcd for $C_{21}H_{23}NO_2S$: C, 71.36; H, 6.56; N, 3.96. Found: C, 71.58; H, 6.35; N, 3.91.

Part C. 6-Methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

A slurry of 600 mg (2.20 mmol) of 4-[2-(1-pyrrolidinyl)ethoxy]benzoic acid hydrochloride in 20 mL of 1,2-dichloroethane and 2 drops of DMF was treated with 0.8 mL (11.0 mmol) of $SOCl_2$ and the mixture was heated to mild

reflux for 2 h. The clear solution was evaporated *in vacuo*, the residue was re-suspended in 20 mL of 1,2-dichloroethane, and the mixture was re-concentrated. The solid was suspended in 20 mL of 1,2-dichloroethane and the mixture cooled to 0 °C. 1-[2-[4-(6-Methoxybenzo[*b*]thiophen-2-yl)phenoxy]-ethyl]pyrrolidine (part B; 650 mg, 1.97 mmol) was added to the acid chloride solution, followed by 2.10 g (15.7 mmol) of $AlCl_3$ in two portions. The mixture was stirred at 0 °C for 5 h at which time it was carefully poured into 200 mL of a 0 °C solution of saturated aq $NaHCO_3$. The mixture was extracted with EtOAc (4 x 100 mL). The combined organic extracts were dried over K_2CO_3 and evaporated *in vacuo* to give 735 mg of an oil. Purification by radial chromatography (SiO_2; 10% MeOH in CH_2Cl_2) afforded 330 mg (0.58 mmol; 26%) of the title compound as a viscous oil. A sample of the pure product (70 mg; 0.12 mmol) in 5 mL of EtOAc was treated with a solution of 25 mg (0.28 mmol; 2.3 eq) of oxalic acid in 3.0 mL EtOAc. The resulting solid was filtered, dried and characterized.

FDMS 571 (M+1); Anal. Calcd for $C_{34}H_{38}N_2O_4S \cdot 2C_2H_2O_4 \cdot H_2O$: C, 59.37; H, 5.77; N, 3.64. Found: C, 59.67; H, 5.56; N, 3.73.

Part D. 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 4-[2-(1-Pyrrolidinyl)-ethoxy]phenyl Ketone Dioxalate.

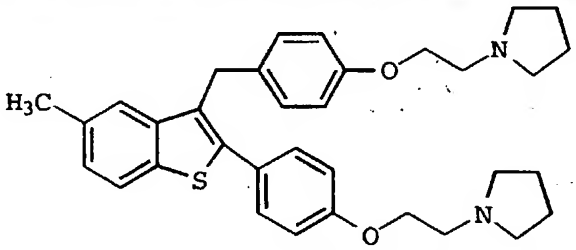
A 0 °C solution of 250 mg (0.45 mmol) of 6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[2-(1-pyrrolidinyl)ethoxy]phenyl ketone (Part C) in 10 mL of 1,2-dichloroethane was treated with 360 mg (2.7 mmol) of $AlCl_3$, followed by 0.28 mL (3.8 mmol) of ethanethiol. The cold bath was removed and the reaction was stirred at room temperature for 10 h. The reaction mixture was poured into 200 mL of a 1:1 mixture of EtOAc and saturated aq $NaHCO_3$ with 10 mL MeOH rinse. The two layers were separated and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined EtOAc layers were dried over Na_2SO_4 and evaporated to

give 325 mg of an oil. Purification by radial chromatography (SiO_2; gradient of 10% MeOH in CH_2Cl_2 to 20% MeOH and 1% TEA in CH_2Cl_2) afforded 130 mg (0.23 mmol, 52%) of an amorphous solid. The solid was converted to the dioxalate salt according to the conditions outlined in Example 1, Part C.

^{1}H NMR (DMSO-d_6) δ 9.77 (s, 1H), 7.63 (dd, J = 8.8, 1.7 Hz, 2H), 7.31 (d, J = 2.1 Hz, 1H), 7.24 (d, J = 8.7 Hz, 2H), 7.19 (s, 1H), 6.95-6.79 (m, 5H) 4.05 (t, J = 6.0 Hz, 2H), 3.98 (t, J = 5.6 Hz, 2H), 2.78-2.63 (m, 4H), 2.53-2.37 (m, 8H) 1.66-1.57 (m, 8H); FDMS 557 (M+1; 100); Anal. Calcd for: C, 60.32; H, 5.47; N, 3.80. Found: C, 60.21; H, 5.63; N, 3.69.

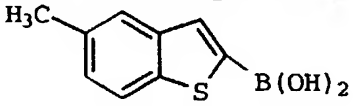
Example 2

Preparation of 1-[2-[4-[[5-Methyl-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl]-methyl]phenoxy]ethyl]pyrrolidine Dioxalate.



2 $C_2H_2O_4$

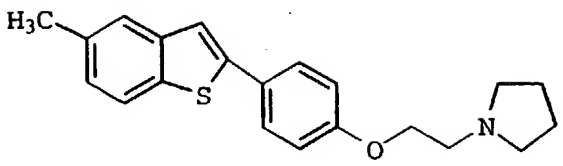
Part A. 5-Methylbenzo[*b*]thiophene-2-boronic Acid.



The title compound was prepared from 5-methyl-benzo[*b*]thiophene as a white solid in 51% yield by essentially following the procedure described in Example 1, Part A.

mp > 250 °C; FDMS: 192 (M^+).

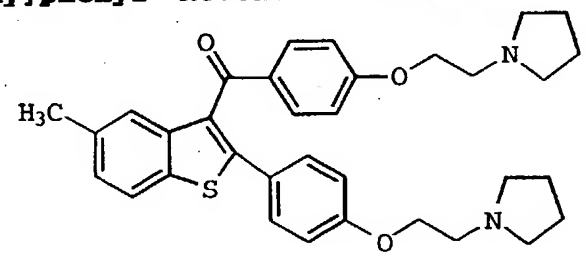
Part B. 5-Methyl-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene.



The title compound was prepared from 5-methyl-benzo[*b*]thiophene-2-boronic acid as a light yellow solid in a 44% yield by essentially following the procedure described in Example 1, Part B.

mp 149.5-151.0 °C; FDMS 337 (M^+; 100); Anal. Calcd for $C_{21}H_{23}NOS$: C, 74.74; H, 6.87; N, 4.15. Found: C, 74.94; H, 6.82; N, 4.31.

Part C. 5-Methyl-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl [4-[2-(1-Pyrrolidinyl)-ethoxy]phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

A slurry of 665 mg (2.45 mmol) of 4-[2-(1-pyrrolidinyl)ethoxy]benzoic acid hydrochloride in 20 mL of 1,2-dichloroethane and 2 drops of DMF was treated with 0.90 mL (12.3 mmol) of $SOCl_2$ and the mixture was heated to gentle reflux for 2.5 h. The resulting solution was evaporated *in vacuo*, the residue was re-suspended in 20 mL of 1,2-dichloroethane, and the mixture was re-concentrated. The solid was suspended in 20 mL of 1,2-dichloroethane and to this was added at 0 °C 5-methyl-2-[4-[2-(1-pyrrolidinyl)ethoxy)-phenyl]benzo[*b*]thiophene (part B; 750 mg, 2.22 mmol). The reaction was protected from light and 1.2 mL (10.9 mmol) $TiCl_4$ was added dropwise. The reaction was stirred at 0 °C for 3 h at which time it was quenched by the careful addition of 25 mL of saturated aq $NaHCO_3$. The mixture was filtered through diatomaceous earth, and the two layers were

separated. The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over K_2CO_3 and evaporated *in vacuo* to give 1.34 g of crude product which was purified by radial chromatography (SiO_2; 10% MeOH in CH_2Cl_2) to afford 980 mg (1.77 mmol; 80%) of the title compound as a viscous oil. A 210 mg sample of this material was converted to the dioxalate salt according to the methods described in Example 1, Part C.

^1H NMR (DMSO-d_6) δ 7.98 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.6 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H). 7.34-7.24 (m, 2H), 7.06-6.94 (m, 4H), 4.38-4.21 (m, 4H), 3.59-3.46 (m, 4H), 3.36-3.22 (m, 8H), 2.36 (s, 3H), 1.98-1.84 (m, 8H); FDMS 555 (M+1); 645 (M+91; 100); Anal. Calcd for $C_{34}H_{38}N_2O_3S \cdot 2C_2H_2O_4 \cdot 0.5H_2O$: C, 61.36; H, 5.83; N, 3.77. Found: C, 61.35; H, 6.04; N, 3.97.

Part D. 1-[2-[4-[[5-Methyl-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl]methyl]phenoxy]-ethyl]pyrrolidine Dioxalate.

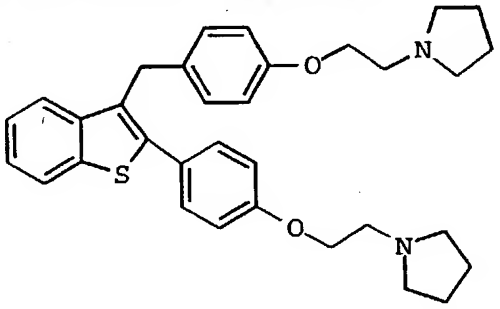
A slurry of 160 mg (4.20 mmol) of $LiAlH_4$ in 20 mL THF at 0 °C was treated with a solution of 750 mg (1.35 mmol) of 5-methyl-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]-thiophen-3-yl [4-[2-(1-pyrrolidinyl)ethoxy]phenyl ketone (Example 2, Part C) in 10 mL THF. The reaction was stirred at 0 °C for 2.5 h and was quenched by the sequential addition of 6 mL of H_2O, 6 mL of 2.0 N aq NaOH, and 6 mL of H_2O. The mixture was filtered, the THF was evaporated *in vacuo*, and the resulting aqueous phase was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over K_2CO_3 and concentrated *in vacuo*. The residue was taken up in 5 mL of trifluoroacetic acid (TFA) and the mixture was cooled to 0 °C. Sodium borohydride (100 mg; 2.91 mmol) was carefully added and the reaction stirred for 2 h. The mixture was evaporated *in vacuo*, the residue was taken up in 100 mL EtOAc, and the mixture was washed with saturated aq $NaHCO_3$ (3 x 50 mL). The organic layer was dried over K_2CO_3 and evaporated *in vacuo* to give 675 mg of an oil. Purification

by radial chromatography (SiO_2; 10% MeOH/0.1% TEA in CH_2Cl_2) afforded 550 mg of the title compound as a light yellow oil which was converted to the dioxalate salt according the methods described in Example 1, Part C.

^1H NMR (DMSO-d_6) δ 7.85 (d, J = 8.2 Hz, 1H), 7.48-7.36 (m, 3H), 7.19 (d, J = 8.2 Hz, 1H). 7.10-6.96 (m, 3H), 6.91-6.80 (m, 3H), 4.17 (s, 2H), 4.11 (t, J = 5.8 Hz, 2H), 3.98 (t, J = 5.8 Hz, 2H), 2.81 (t, J = 5.8 Hz, 2H), 2.75 (t, J = 5.8 Hz, 2H), 2.36 (s, 3H), 2.58-2.44 (m, 8H), 1.78-1.60 (m, 8H); FDMS 541 (M+1; 100); Anal. Calcd for $C_{34}H_{40}N_2O_2S \cdot 2C_2H_2O_4 \cdot 0.5H_2O$: C, 62.54; H, 6.21; N, 3.84. Found: C, 62.27; H, 6.16; N, 3.93.

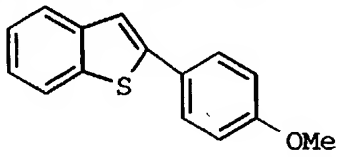
Example 3

Preparation of 1-[2-[4-[[2-[4-[2-(1-Pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl]methyl]phenoxy]-ethyl]pyrrolidine Dioxalate.



2 $C_2H_2O_4$

Part A. 2-(4-Methoxyphenyl)benzo[*b*]thiophene.

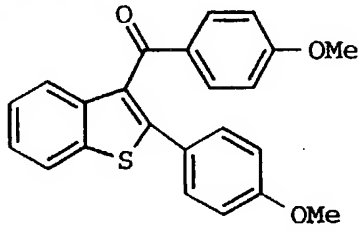


The title compound was prepared in 91% yield from benzo[*b*]thiophene-2-boronic acid and 4-bromoanisole by essentially following the procedure detailed Example 1, Part B.

mp 188-191 °C; ^1H NMR (DMSO-d_6) δ 7.94 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 7.0 Hz, 1H), 7.73 (m, 2H). 7.71 (s, 1H), 7.35 (m, 2H), 7.05 (d, J = 8.0 Hz, 2H), 3.82 (s, 3H); FDMS 240

(M^+; 100); Anal. Calcd for $C_{21}H_{23}NO_2S$: C, 71.36; H, 6.56; N, 3.86. Found: C, 71.46; H, 6.60; N, 3.86.

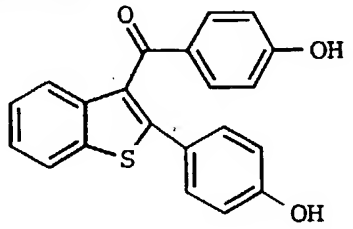
Part B. 2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl 4-Methoxyphenyl Ketone.



The title compound was prepared from 4-anisoyl chloride and 2-(4-methoxyphenyl)benzo[*b*]thiophene (Part A) as a tan solid in 90% yield following recrystallization from THF-hexanes.

FDMS 375 (M+1; 100).

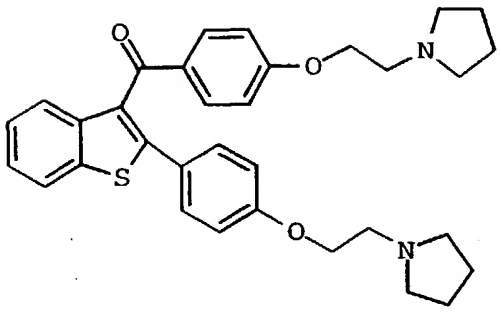
Part C. 2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl 4-Hydroxyphenyl Ketone.



By essentially following the procedure outlined in Example 1, Part D, the title compound was prepared from 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl 4-methoxyphenyl ketone (Part B) as a yellow solid in 93% yield following radial chromatography (SiO_2; gradient of 20-40% EtOAc in hexanes).

FDMS 347 (M+1; 100); Anal. Calcd for $C_{21}H_{14}O_3S$: C, 72.81; H, 4.07. Found: C, 72.57; H, 4.17.

Part D. 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo-[*b*]thiophen-3-yl 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

A solution of 300 mg (0.87 mmol) of 2-(4-hydroxyphenyl)-benzo[*b*]thiophen-3-yl 4-hydroxyphenyl ketone (Part C) in 20 mL of DMF was treated with 880 mg (5.2 mmol) of 1-(2-chloroethyl)pyrrolidine hydrochloride followed by 2.26 g (6.94 mmol) of Cs_2CO_3. The mixture was heated to 80 °C for 6 h at which time it was cooled and filtered. The mother liquor was concentrated *in vacuo* and the residue was partitioned between H_2O (25 mL) and EtOAc (25 mL). The two layers were separated and the aqueous layer was extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over K_2CO_3 and evaporated to give 516 mg of an oil which was purified by radial chromatography (SiO_2; 60:35:5 hexanes-THF-TEA) to afford 371 mg (0.69 mmol; 79%) of an oil. The oil was converted to the dioxalate salt according to the procedure detailed in Example 1, Part C.

FDMS 541 (M+1), 631 (M+91; 100); Anal. Calcd for $C_{33}H_{36}N_2O_3S \cdot 2C_2H_2O_4 \cdot 0.1H_2O$: C, 61.50; H, 5.60; N, 3.88. Found: C, 61.21; H, 5.60; N, 3.91.

Part E. 1-[2-[4-[[2-[4-[2-(1-Pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl]methyl]phenoxy]ethyl]-pyrrolidine Dioxalate.

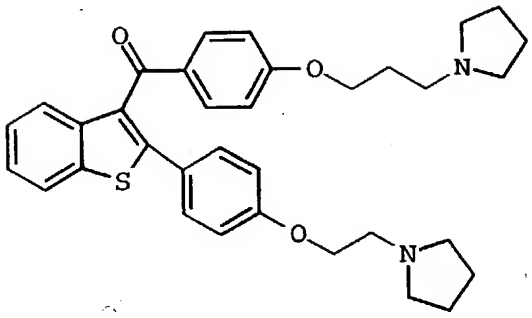
A slurry of 45 mg of $LiAlH_4$ in 10 mL of THF was cooled to 0 °C and was treated with a solution of 200 mg (0.37 mmol) of 2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[2-(1-pyrrolidinyl)ethoxy]phenyl ketone (Part D) in 5 mL of THF. The reaction was stirred at 0 °C for 2 h and was quenched by the sequential addition of 1 mL of H_2O, 1 mL of 2

N aq NaOH, and 1 mL of H_2O. The two layers were separated and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with 25 mL of brine, dried over K_2CO_3, and evaporated *in vacuo*. The residue was taken up in 10 mL of CH_2Cl_2, cooled to 0 °C, and treated with 0.47 mL (2.94 mmol) of triethylsilane. After stirring at 0 °C for 6 h, the reaction was treated with 0.3 mL (3.9 mmol) of TFA, followed by an additional 16 h of stirring at 0 °C. The reaction mixture was poured into 10 mL saturated aq $NaHCO_3$ and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were dried over K_2CO_3 and evaporated *in vacuo* to give 233 mg of an oil which was purified by radial chromatography (SiO_2; gradient 2-10% MeOH in CH_2Cl_2) to afford 158 mg (0.30 mmol; 81%) of the title compound as the free base. Conversion to the dioxalate salt was effected by the procedure detailed in Example 1, Part C.

^1H NMR (DMSO-d_6) δ 7.99 (d, J = 7.8 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.50 (d, J = 8.2 Hz, 2H), 7.43-7.30 (m, 2H), 7.14 (d, J = 8.1 Hz, 2H). 7.06 (d, J = 8.3 Hz, 2H), 6.89 (d, J = 8.1 Hz, 2H), 4.17 (s, 2H), 4.11 (t, J = 5.8 Hz, 2H), 3.98 (t, J = 5.8 Hz, 2H), 2.81 (t, J = 5.8 Hz, 2H), 2.75 (t, J = 5.8 Hz, 2H), 2.36 (s, 3H), 2.58-2.44 (m, 8H), 1.78-1.60 (m, 8H); FDMS 527 (M+1, 100).

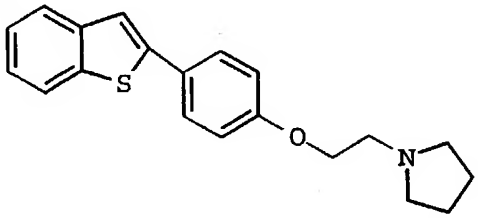
Example 4

Preparation of 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl 4-[3-(1-Pyrrolidinyl)propoxy]-phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

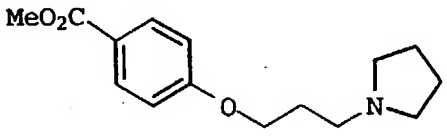
Part A. 1-[2-[4-(Benzo[*b*]thiophen-2-yl)phenoxy]-ethyl]pyrrolidine.



By essentially following the procedure detailed in Example 1, Part B, the title compound was prepared from benzo[*b*]thiophene-2-boronic acid and 1-[2-(4-bromophenoxy)-ethyl]pyrrolidine in 76% yield as a white solid following flash chromatography (SiO_2; 36:4:60 THF-TEA-hexanes).

FDMS 324 (M+1; 100).

Part B. Methyl 4-[3-(1-Pyrrolidinyl)propoxy]benzoate.

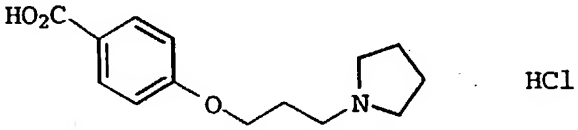


A solution of 6.25 g (23.8 mmol) of triphenylphosphine, 3.30 g (21.7 mmol) of methyl 4-hydroxybenzoate, and 2.80 g (21.7 mmol) of 1-(3-hydroxypropyl)pyrrolidine in 100 mL of CH_2Cl_2 was treated with 3.80 mL (24.1 mmol) of diethyl azodicarboxylate in a dropwise manner. The reaction was stirred at ambient temperature for 16 h and was quenched by the addition of 20 mL of brine. The two layers were separated, and the organic layer was dried over K_2CO_3 and

concentrated to give 6.10 g of an oily solid which was purified by flash chromatography (SiO_2; 0-5% MeOH in CH_2Cl_2) to afford 2.46 g (9.34 mmol; 43%) of the desired product.

FDMS 263 (M^+; 100); HRMS Calcd for $C_{15}H_{21}NO_3$: 264.1600. Found: 264.1609.

Part C. 4-[3-(1-Pyrrolidinyl)propoxy]benzoic Acid Hydrochloride.



A solution of 2.0 g (7.6 mmol) of the methyl 4-[3-(1-pyrrolidinyl)propoxy]benzoate (Part B) in 90 mL of THF was treated with 90 mL of 0.1 N aq LiOH for 48 h. The THF was evaporated *in vacuo*. The aqueous phase was adjusted to pH 11 with 1.0 N aq HCl and was applied to column of Biorad AG1-X8 Resin (100-200 mesh; acetate form) which had been prewashed with 2 L of 2.0 N aq NaOH. The column was sequentially eluted with 1 L of H_2O, 1 L of 50% THF in H_2O, 1 L of H_2O and 2 L of 3.0 N aq AcOH. The acidic fraction was evaporated *in vacuo*, the residue was reconstituted in 20 mL of 1.0 N aq HCl and the mixture was frozen. Lyophilization afforded 1.50 g (3.9 mmol; 51%) of the desired product as a white powder.

FDMS 249 (M^+; 100); Anal. Calcd for $C_{14}H_{19}NO_3 \cdot HCl$: C, 58.84; H, 7.05; N, 4.90. Found: C, 58.58; H, 6.85; N, 5.13.

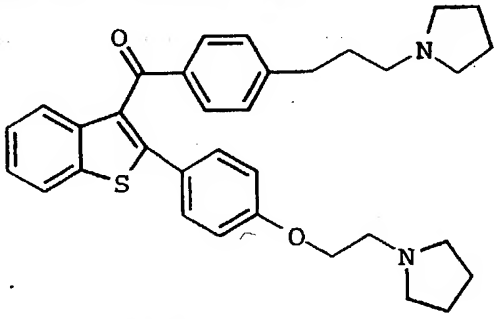
Part D. 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl 4-[3-(1-Pyrrolidinyl)propoxy]-phenyl Ketone Dioxalate.

The title compound was prepared from 4-[3-(1-pyrrolidinyl)propoxy]benzoic acid hydrochloride (Part C) and 1-[2-[4-(benzo[*b*]thiophen-2-yl)phenoxy]ethyl]pyrrolidine (Part A) in 55% yield by essentially following the procedure outlined in Example 2, Part C.

^{1}H NMR (DMSO-d_6) δ 8.11 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 8.7 Hz, 2H), 7.48-7.33 (m, 5H), 7.01 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 4.30 (t, J = 3.8 Hz, 2H), 4.11 (t, J = 5.2 Hz, 2H), 3.54 (t, J = 4.2 Hz, 2H), 3.43-3.15 (m, 8H), 2.18-2.05 (m, 2H), 2.02-1.85 (m, 10H); FDMS 555 (M+1; 100); Anal. Calcd for $C_{34}H_{38}N_2O_3S \cdot 2C_2H_2O_4$: C, 62.11; H, 5.76; N, 3.81. Found: C, 62.08; H, 5.76; N, 3.84.

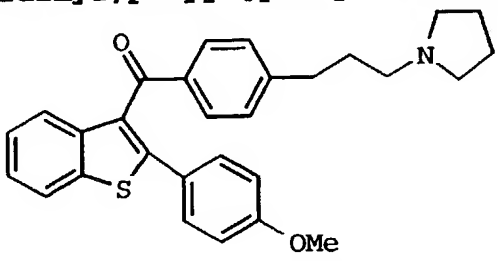
Example 5

Preparation of 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]-thiophen-3-yl 4-[3-(1-Pyrrolidinyl)propyl]-phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

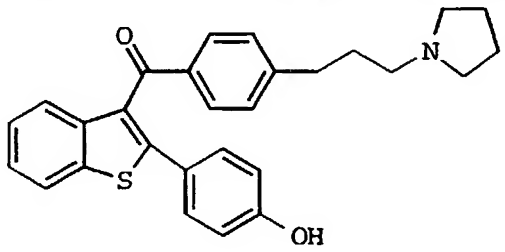
Part A. 2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl 4-[3-(1-Pyrrolidinyl)propyl]phenyl Ketone.



By essentially following the procedure outlined in Example 2, Part C, the title compound was prepared from 2-(4-methoxyphenyl)benzo[*b*]thiophene (Example 3; Part A) and 4-[3-(1-pyrrolidinyl)propyl]benzoic acid hydrochloride in 33% yield as a viscous oil.

FDMS 456 (M+1; 100); Anal. Calcd for $C_{29}H_{29}NO_2S$: C, 76.45; H, 6.42; N, 3.07. Found: C, 76.21; H, 6.39; N, 3.14.

Part B. 2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl 4-[3-(1-Pyrrolidinyl)propyl]phenyl Ketone.



A 100 mL round bottom flask containing 300 mg (0.66 mmol) of 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl 4-[3-(1-pyrrolidinyl)propyl]phenyl ketone (Part A) was filled with 20 g of pyridine hydrochloride. The flask was heated to 160 °C to melt the solid. After 16 h, the reaction was cooled to warm temperature, diluted with 50 mL of H_2O, and transferred to separatory funnel containing 50 mL H_2O and 50 mL of EtOAc. The two layers were separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined EtOAc layers were dried over Na_2SO_4 and concentrated *in vacuo* to give 325 mg of a yellow oil. Purification by radial chromatography (SiO_2; gradient of 2-10% MeOH in CH_2Cl_2) afforded 200 mg (0.45 mmol; 69%) of the title compound as a viscous yellow oil.

FDMS 441 (M^+; 100); Anal. Calcd for $C_{28}H_{27}NO_2S$: C, 76.16; H, 6.16; N, 3.17. Found: C, 76.59; H, 6.27; N, 3.07.

Part C. 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl 4-[3-(1-Pyrrolidinyl)propyl]-phenyl Ketone Dioxalate.

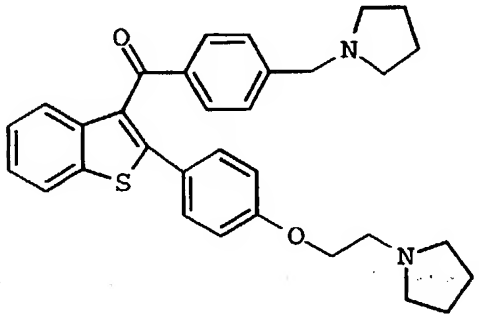
By essentially following the procedure outlined in Example 3, Part D, the free base of the title compound was prepared from 2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl 4-[3-(1-pyrrolidinyl)propyl]phenyl ketone (Part B) and 1-(2-chloroethyl)pyrrolidine hydrochloride in 36% yield as a viscous oil following radial chromatography (SiO_2; gradient of 5-15% MeOH in CH_2Cl_2). The free base was converted to the

dioxalate salt according to the conditions described in Example 1, Part C.

^{1}H NMR (DMSO-d_6) δ 8.12 (d, J = 7.8 Hz, 1H), 7.69 (d, J = 7.9 Hz, 2H), 7.45-7.34 (m, 7H), 7.30 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 8.4 Hz, 2H), 4.32-4.21 (m, 2H), 3.57-3.43 (m, 2H), 3.35-3.12 (m, 8H), 3.07 (t, J = 6.2 Hz, 2H), 2.66 (t, J = 6.5 Hz, 2H), 2.04-1.80 (m, 10H); FDMS 539 (M+1; 66); Anal. Calcd for $C_{34}H_{38}N_2O_2S \cdot 2C_2H_2O_4$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.75; H, 6.12; N, 3.85.

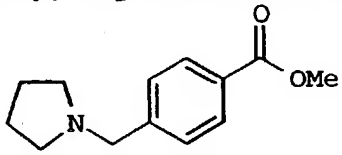
Example 6

2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[(1-Pyrrolidinyl)methyl]phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

Part A. Methyl 4-[(1-Pyrrolidinyl)methyl]benzoate.

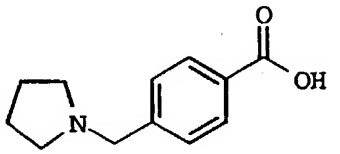


A solution of 6.20 mL (44.5 mmol) of TEA and 4.70 g (21.8 mmol) of 4-carboxybenzyl bromide in 50 mL of DMF was treated with 2.10 mL (25.2 mmol) of pyrrolidine at 50 °C for 3 h. The reaction mixture was cooled, evaporated *in vacuo*, and the residue was taken up in 50 mL of MeOH. The solution was treated with a rapid stream of HCl (g) for 15 min, the reaction vessel was sealed and the reaction stirred at ambient temperature for 16 h. Evaporation of the solvent afforded 2.56 g of an oil which was purified by radial

chromatography (SiO_2; 80:18:2 hexanes-THF-TEA) to afford 2.30 g (10.5 mmol; 48%) of the title compound as an oil.

FDMS 219 (M^+; 100)

Part B. 4-[(1-Pyrrolidinyl)methyl]benzoic Acid Hydrochloride.



HCl

By essentially following the procedure outlined in Example 4, Part C, the title compound was prepared from methyl 4-[(1-pyrrolidinyl)methyl]benzoate in 22% yield as a white solid following ion exchange chromatography.

FDMS 206 (M+1; 100); Anal. Calcd for $C_{12}H_{15}NO_2 \cdot HCl$. 0.2 H_2O: C, 58.75; H, 6.74; N, 5.71. Found: C, 58.95; H, 6.56; N, 5.54.

Part C. 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl 4-[(1-Pyrrolidinyl)methyl]phenyl Ketone Dioxalate.

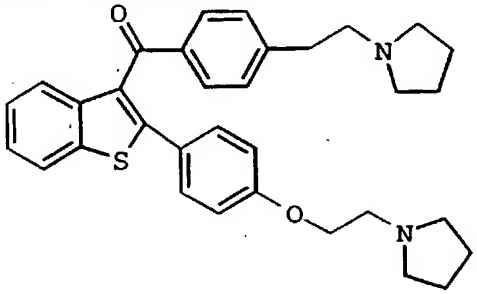
By essentially following the procedure outlined in Example 2, Part C, the free base of the title compound was prepared from 4-[(1-pyrrolidinyl)methyl]benzoic acid hydrochloride (Part B) and 1-[2-[4-(benzo[*b*]thiophen-2-yl)phenoxy]ethyl]pyrrolidine (Example 4, Part A) in 44% yield. The free base was converted to the dioxalate salt according to the conditions described in Example 1, Part C.

^1H NMR (DMSO-d_6) δ 8.10 (dd, J = 6.5, 1.8 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.63 (d, J = 8.5 Hz, 1H), 7.52-7.36 (m, 4H), 7.32 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 4.27-4.15 (m, 4H), 3.53-3.43 (m, 2H), 3.34-3.20 (m, 4H), 3.20-2.94 (m, 4H), 1.96-1.80 (m, 8H); FDMS 510 (M^+; 100); Anal. Calcd for

$C_{32}H_{34}N_2O_2S \cdot 2C_2H_2O_4$: C, 62.60; H, 5.54; N, 4.06. Found: C, 62.79; H, 5.56; N, 4.00.

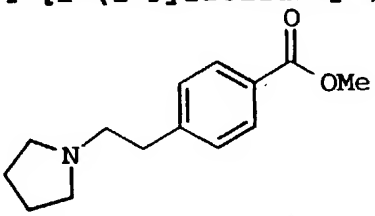
Example 7

Preparation of 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl 4-[2-(1-Pyrrolidinyl)ethyl]-phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

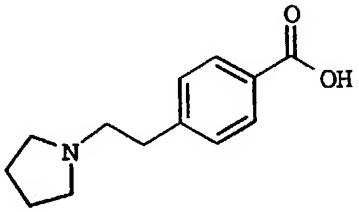
Part A. Methyl 4-[2-(1-Pyrrolidinyl)ethyl]benzoate.



By essentially following the procedure detailed in Example 6, Part A, the title compound was prepared from 4-[2-bromoethyl)benzoic acid and pyrrolidine in 39% yield as an oil following radial chromatography (SiO_2; 89:9:2 hexanes-THF-TEA).

FDMS 234 (M+1; 100)

Part B. 4-[2-(1-Pyrrolidinyl)ethyl]benzoic Acid Hydrochloride.



HCl

By essentially following the procedure outlined in Example 4, Part C, the title compound was prepared from methyl 4-[2-(1-pyrrolidinyl)ethyl]benzoate (Part A) in 24% yield as a white solid following ion exchange chromatography.

FDMS 220 (M+1; 100); Anal. Calcd for $C_{13}H_{17}NO_2 \cdot HCl \cdot 0.1H_2O$: C, 60.63; H, 7.12; N, 5.44. Found: C, 60.48; H, 7.08; N, 5.32.

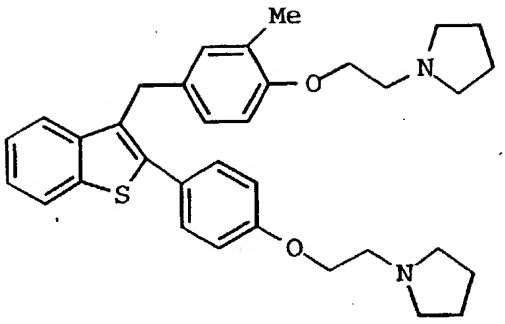
Part C. 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl 4-[2-(1-Pyrrolidinyl)ethyl]-phenyl Ketone Dioxalate.

By essentially following the procedure outlined in Example 2, Part C, the free base of the title compound was prepared from 4-[2-(1-pyrrolidinyl)ethyl]benzoic acid hydrochloride (Part B) and 1-[2-[4-(benzo[*b*]thiophen-2-yl)phenoxy]ethyl]pyrrolidine (Example 4, Part A) in 45% yield. The free base was converted to the dioxalate salt according to the conditions described in Example 1, Part C.

^{1}H NMR (DMSO-d_6) δ 8.10 (dd, J = 6.4, 2.0 Hz, 1H), 7.72-7.61 (m, 3H), 7.45-7.39 (m, 4H), 7.31 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.27-4.04 (m, 4H), 3.53-3.40 (m, 2H), 3.31-3.17 (m, 4H), 3.10-2.92 (m, 2H), 2.87-2.64 (m, 2H), 1.99-1.72 (m, 8H), 1.55-1.40 (m, 2H); FDMS 524 (M^+; 100); Anal. Calcd for $C_{33}H_{36}N_2O_2S \cdot 2C_2H_2O_4$: C, 63.06; H, 5.72; N, 3.97. Found: C, 63.33; H, 5.67; N, 3.90.

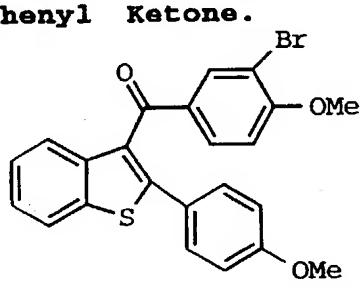
Example 8

Preparation of 1-[2-[2-Methyl-4-[2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-ylmethyl]-phenoxy]ethyl]pyrrolidine Dioxalate.



2 $C_2H_2O_4$

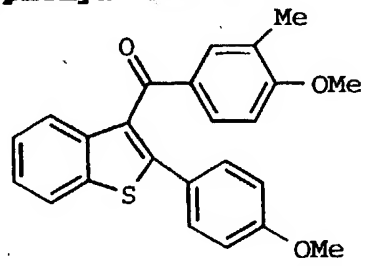
Part A. 2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl 3-Bromo-4-methoxyphenyl Ketone.



The title compound was prepared in 76% yield from 2-(4-methoxyphenyl)]benzo[*b*]thiophene (Example 3, Part A) and 3-bromo-4-methoxybenzoic acid by essentially following the procedures detailed in Example 2, Part C.

^{1}H NMR (DMSO-d_6) δ 8.12 (d, J = 7.3 Hz, 1H), 7.91 (s, 1H), 7.69 (dd, J = 8.7, 1.8 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.52-7.41 (m, 2H), 7.37 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 8.7 Hz, 1H), 6.94 (d, J = 8.6 Hz, 2H), 3.89 (s, 3H), 3.75 (s, 3H); FDMS 452 (M-1), 454 (M+1).

Part B. 2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl 3-Methyl-4-methoxyphenyl Ketone.

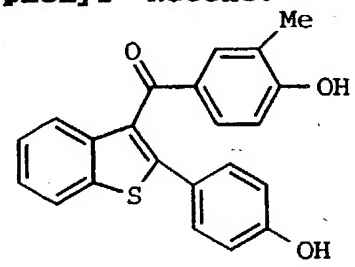


A slurry of 750 mg (1.65 mmol) of 2-(4-methoxyphenyl)-benzo[*b*]thiophen-3-yl 3-bromo-4-methoxyphenyl ketone (Part A)

in 15 mL of toluene was treated with 75 mg (0.07 mmol) of tetrakis(triphenylphosphine)palladium(0) and 0.54 mL (3.9 mmol) of tetrabutyltin. The tube was sealed and the contents were heated at 130 °C for 15 h. The reaction was cooled, evaporated *in vacuo*, and the residue was taken up in 75 mL of Et_2O. Saturated aq KF (75 mL) was added and the mixture was stirred vigorously for 6 h. The two layers were separated and the organic layer was washed with H_2O (3 x 75 mL). The organic phase was dried over Na_2SO_4 and evaporated *in vacuo* to give 934 mg of an oil which was purified by radial chromatography (SiO_2; 25% EtOAc in hexanes) to afford 602 mg (1.55 mmol; 94%) of the title compound as a white solid.

FDMS 388 (M^+), 389 (M+1); HRMS calcd for $C_{24}H_{21}O_3S$, 389.1211. Found 389.1180.

Part C. 2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl 3-Methyl-4-hydroxyphenyl Ketone.

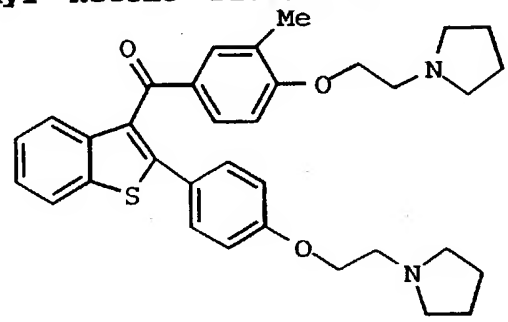


A 0 °C solution of 700 mg (1.80 mmol) of 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl 3-methyl-4-methoxyphenyl ketone (Part B) in 25 mL of CH_2Cl_2 was treated with 7.2 mL of BBr_3 (1.0 M in CH_2Cl_2). The reaction was stirred at 0 °C for 6 h, then cooled to -78 °C, and was treated carefully with 50 mL of MeOH. The mixture was allowed to warm to room temperature over 1.5 h, and the volatiles were evaporated *in vacuo*. The dark red residue (monomethyl ether) was taken up in 75 mL dichloroethane and was treated with $AlCl_3$ and ethanethiol according to the conditions of Example 1, Part D to afford 675 mg of an oil. Purification by radial chromatography (SiO_2; gradient of 20-30% EtOAc in hexanes)

afforded 410 mg (1.14 mmol; 63%) of the title compound as an orange solid.

FDMS 360 (M^+); Anal. Calcd for $C_{22}H_{16}O_3S$: C, 73.31; H, 4.47. Found: C, 73.57; H, 4.66.

Part D. 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl 3-Methyl-4-[2-(1-pyrrolidinyl)-ethoxy]phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

By essentially following the procedure detailed in Example 3, Part D, the free base of the title compound was prepared from 2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl 3-methyl-4-hydroxyphenyl ketone (Part C) and 1-(2-chloroethyl)pyrrolidine hydrochloride in 83% yield as an oil following radial chromatography (SiO_2; 10% MeOH and 0.5% TEA in CH_2Cl_2). The free base was converted to the dioxalate salt according to the conditions described in Example 1, Part C.

^1H NMR (DMSO-d_6) δ 8.10 (d, J = 7.8 Hz, 1H), 7.64 (s, 1H), 7.56-7.34 (m, 6H), 7.00-6.92 (m, 3H). 4.13 (t, J = 5.4 Hz, 2H), 4.08 (t, J = 5.7 Hz 2H), 2.95-2.78 (m, 4H) 2.68-2.56 (m, 8H), 2.12 (s, 3H), 1.78-1.64 (m, 8H); FDMS 555 (M^+; 100); HRMS $C_{34}H_{39}N_2O_3S$: 555.2681. Found: 555.2706.

Part E. 1-[2-[2-Methyl-4-[2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-ylmethyl]phenoxy]-ethyl]pyrrolidine Dioxalate.

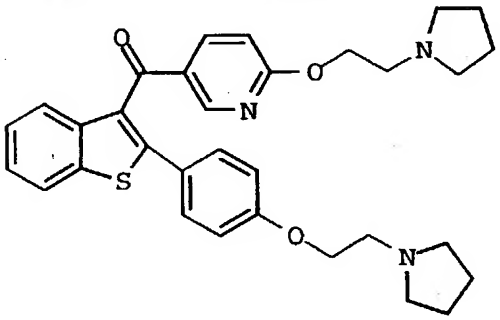
By essentially following the conditions detailed in Example 2; Part D, the free base of the title compound was

prepared from 2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]-thiophen-3-yl 3-methyl-4-[2-(1-pyrrolidinyl)ethoxy]phenyl ketone (Part D) in 88% yield as an oil following radial chromatography (SiO_2; 10% MeOH and 0.5% TEA in CH_2Cl_2). The free base was converted to the dioxalate salt according to the conditions described in Example 1, Part C.

^1H NMR (DMSO-d_6) δ 8.04-7.95 (m, 1H), 7.64-7.56 (m, 1H), 7.51 (d, J = 8.1 Hz, 2H), 7.42-7.32 (m, 2H). 7.14 (d, J = 8.2 Hz, 2H), 6.97 (s, 1H), 6.92-6.80 (m, 2H), 4.36 (t, J = 4.8 Hz, 2H), 4.22 (t, J = 5.0 Hz 2H), 4.18 (s, 2H), 2.95-2.78 (m, 4H) 2.68-2.56 (m, 8H), 2.12 (s, 3H), 1.78-1.64 (m, 8H); FDMS 541 (M^+; 100), 631 ($M^+ + C_2H_2O_4$); Anal. Calcd for $C_{34}H_{40}N_2O_2S \cdot 2C_2H_2O_4 \cdot 1.9H_2O$: C, 63.78; H, 6.20; N, 3.93. Found: C, 63.81; H, 6.47; N, 3.82.

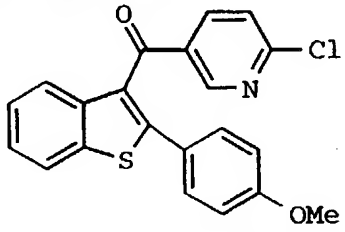
Example 9

Preparation of 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl 6-[2-(1-Pyrrolidinyl)ethoxy]-pyrid-3-yl Ketone Dioxalate.



2 $C_2H_2O_4$

Part A. 2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl 6-Chloro-pyrid-3-yl Ketone.

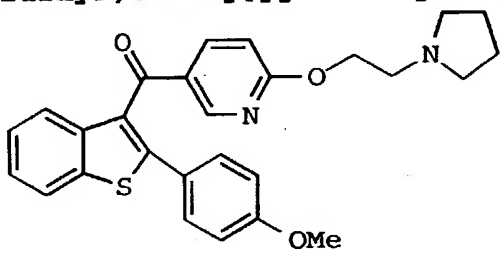


By essentially following the procedure detailed in Example 1, Part C, the title compound was prepared from 6-

chloronicotinic acid and 2-(4-methoxyphenyl)benzo[*b*]thiophene (Example 3, Part A) in 31% yield as a yellow solid following flash chromatography (SiO_2; CH_2Cl_2).

FDMS 379 (M^+, 100), 381; Anal. Calcd for $C_{21}H_{14}ClNO_2S$: C, 66.40; H, 3.71; N, 3.69. Found: C, 66.20; H, 3.71; N, 3.79.

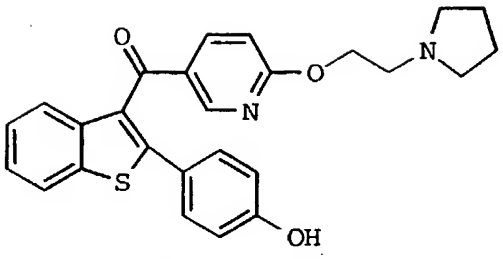
Part B. 2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl 6-[2-(1-Pyrrolidinyl)ethoxy]pyrid-3-yl Ketone.



A solution of 0.50 mL (4.30 mmol) of 1-(2-hydroxyethyl)-pyrrolidine in 10 mL of xylenes was treated with 50 mg (2.20 mmol) of Na. The mixture was heated to 50 °C until all the Na had disappeared, cooled to room temperature, and then treated with a solution of 420 mg (1.10 mmol) of 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl 6-chloropyrid-3-yl ketone (Part A) in 5 mL of xylenes. The reaction was heated to 50 °C for 2 h and was evaporated *in vacuo*. The residue was partitioned between H_2O (50 mL) and EtOAc (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over K_2CO_3 and evaporated *in vacuo* to give 810 mg of a yellow solid. Purification by radial chromatography (SiO_2; gradient of 1-5% MeOH in CH_2Cl_2) gave 525 mg (1.09 mmol; 99%) of the title compound as an amber oil.

FDMS 459 (M^+; 100); Anal. Calcd for $C_{27}H_{26}N_2O_3S$: C, 70.72; H, 5.71; N, 6.11. Found: C, 70.43; H, 5.60; N, 6.02.

Part C. 2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl 6-[2-(1-Pyrrolidinyl)ethoxy)pyrid-3-yl Ketone.



By essentially following the procedures outlined in Example 1, Part D, the title compound was prepared from 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl 6-[2-(1-pyrrolidinyl)-ethoxy]pyrid-3-yl ketone (Part B) in 89% yield as a yellow solid following radial chromatography (SiO_2, 5% MeOH in CH_2Cl_2).

FDMS 445 (M+1; 100); HRMS calcd for $C_{26}H_{25}N_2O_3S$: 445.1586. Found: 445.1569.

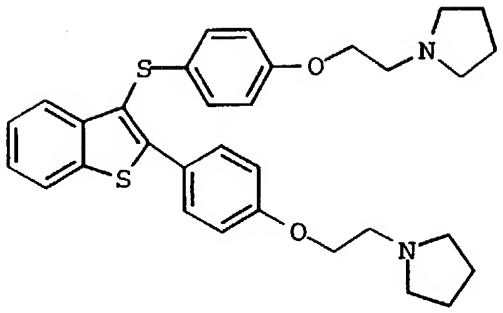
Part D. 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl 6-[2-(1-Pyrrolidinyl)ethoxy]-pyrid-3-yl Ketone Dioxalate.

By essentially following the procedure detailed in Example 3, Part D, the free base of the title compound was prepared from 2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl 6-[2-(1-pyrrolidinyl)ethoxy)pyrid-3-yl ketone (Part C) and 1-(2-chloroethyl)pyrrolidine hydrochloride in 84% yield as an oil following radial chromatography (SiO_2; gradient of 5-20% MeOH in THF). The free base was converted to the dioxalate salt according to the conditions described in Example 1, Part C.

FDMS 542 (M+1); Anal. Calcd for $C_{32}H_{35}N_3O_3S \cdot 2C_2H_2O_4 \cdot 1.5H_2O$: C, 57.74; H, 5.65; N, 5.61. Found: C, 57.68; H, 5.42; N, 5.49.

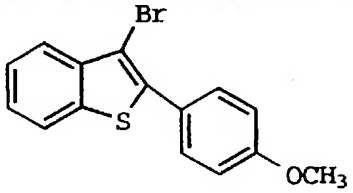
Example 10

Preparation of 1-[2-[4-[[2-[4-[2-(1-Pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl]thio]phenoxy]-ethyl]pyrrolidine Dioxalate.



2 $C_2H_2O_4$

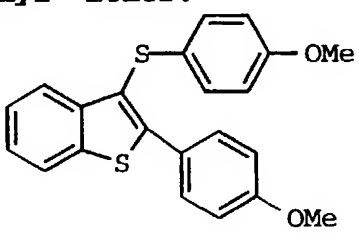
Part A. 3-Bromo-2-(4-methoxyphenyl)benzo[*b*]thiophene.



A slurry of 5.0 g (20.8 mmol) of 2-(4-methoxyphenyl)-benzo[*b*]thiophene (Example 3, Part A) in 400 mL of $CHCl_3$ at 0 °C was treated slowly with 1.6 mL of Br_2, resulting in a yellow solution. The reaction was stirred at 0 °C for 1 h and then washed sequentially with 200 mL of 1.0 N aq $Na_2S_2O_3$, 200 mL of 1.0 N aq $NaHCO_3$, and 200 mL of H_2O. After drying over Na_2SO_4, evaporation of the solvent *in vacuo* gave 6.24 g (19.5 mmol; 94%) of an off-white solid which was clean by thin layer chromatography.

mp 84.5-86.5 °C; ^1H NMR ($CDCl_3$) δ 7.86 (d, J = 7.9 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.72 (d, J = 8.7 Hz, 2H), 7.50-7.37 (m, 2H), 7.02 (d, J = 8.7 Hz, 2H), 3.88 (s, 3H); FDMS 318 (100), 320 (M+1); Anal. Calcd For $C_{15}H_{11}BrOS$: C, 56.44; H, 3.47. Found: C, 56.25; H, 3.38.

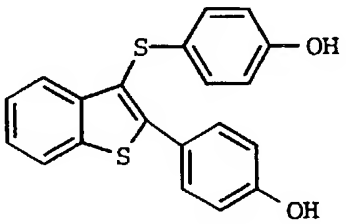
Part B. Methyl 4-[[2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl]thio]phenyl Ether.



To a solution of 1.0 g (3.1 mmol) of 3-bromo-2-(4-methoxyphenyl)benzo[*b*]thiophene (Part A) in 20 mL of THF was added dropwise 2.9 mL of 1.6 M *n*-BuLi in hexanes (4.7 mmol) at -70 °C. The mixture was stirred at -70 °C for 10 min and then treated with 0.87 g (3.13 mmol) of solid bis(4-methoxyphenyl)disulfide. Stirring was continued at -70 °C for 0.5 h and then the reaction was allowed to warm slowly to room temperature. The reaction was quenched with 1 mL of saturated aq NH_4Cl and 1 mL of MeOH and was concentrated *in vacuo*. The residue was partitioned between 100 mL of EtOAc and 100 mL of H_2O. The organic layer was separated, dried over $MgSO_4$, and concentrated *in vacuo* to afford an oily solid which was subjected to flash chromatography (SiO_2; gradient of 1-5% EtOAc in hexanes) to afford 0.82 g of the title compound as an oil.

FDMS 378 (M+1; 100).

Part C. 4-[[2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl]thio]phenol.



A solution of 0.82 g (2.2 mmol) of methyl 4-[[2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl]thio]phenyl ether (Part B) in 50 mL of dichloroethane was treated with 1.2 mL (3.3 g; 13 mmol) of BBr_3 at 0 °C for 5 h. The reaction was quenched by the careful addition of 15 mL of MeOH. Evaporation of the solvent *in vacuo* gave a residue which was subjected to flash chromatography (SiO_2; 1% MeOH in $CHCl_3$) to afford 0.47 g of the desired product as a solid.

FDMS 350 (M^+; 100); Anal. Calcd For $C_{20}H_{14}O_2S_2 \cdot 0.5MeOH$: C, 67.19; H, 4.40. Found: C, 67.04; H, 4.25.

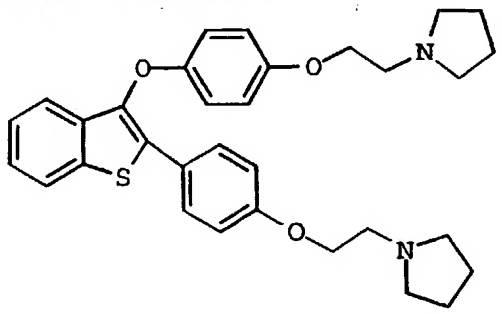
Part D. 1-[2-[4-[[2-[4-[2-(1-Pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl]thio]phenoxy]ethyl]-pyrrolidine Dioxalate.

By essentially following the procedure detailed in Example 4, Part B, except using 1-(2-hydroxyethyl)-pyrrolidine, the free base of the title compound was prepared from 4-[[2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl]thio]phenol (Part C) and 1-(2-hydroxyethyl)pyrrolidine in 43% yield as an oil following radial chromatography (SiO_2; 3% TEA and 37% THF in hexanes). The free base was converted to the dioxalate salt according to the conditions described in Example 1, Part C.

^1H NMR (DMSO-d_6) δ 8.12-8.00 (m, 1H), 7.76-7.65 (m, 3H), 7.47-7.38 (m, 2H), 7.13 (d, J = 8.8 Hz, 2H), 7.00 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.9 Hz, 2H), 4.36 (t, J = 5.0 Hz, 2H), 4.19 (d, J = 5.1 Hz, 2H), 3.56 (t, J = 4.8 Hz, 2H), 3.47 (t, J = 4.9 Hz, 2H), 3.42-3.18 (m, 8H), 2.03-1.82 (m, 8H); FDMS 545 (M+1), 636 (M+91, 100); Anal. Calcd For $C_{32}H_{36}N_2O_2S_2 \cdot 2C_2H_2O_4 \cdot 0.4H_2O$: C, 59.07; H, 5.62; N, 3.83. Found: C, 59.02; H, 5.49; N, 4.22.

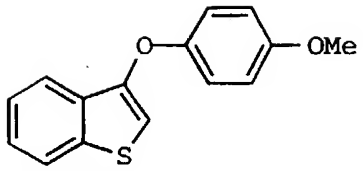
Example 11

Preparation of 1-[2-[4-[3-[4-[2-(1-Pyrrolidinyl)-ethoxy]phenoxy]benzo[*b*]thiophen-2-yl]phenoxy]ethyl]-pyrrolidine Dioxalate.



2 $C_2H_2O_4$

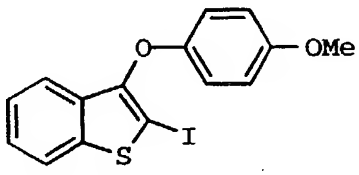
Part A. Benzo[*b*]thiophen-3-yl 4-Methoxyphenyl Ether.



A mixture of 4.00 g (19.7 mmol) of 3-bromobenzo[*b*]-thiophene, 4.96 g (40 mmol) of 4-methoxyphenol, 5.52 g (40 mmol) of K_2CO_3, and 0.20 g (1.0 mmol) of CuI was heated to 140 °C and sonicated at this temperature for 2 h. The reaction was allowed to cool, taken up in CH_2Cl_2, and the mixture was washed several times with 0.5 N NaOH. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to an oil that was subjected to chromatography (SiO_2; gradient of 0-5% EtOAc in hexanes). The fractions containing the desired product were combined, evaporated *in vacuo*, and the residue was recrystallized from hexanes to afford 500 mg (1.95 mmol; 10%) of the title compound as a white solid.

Anal. Calcd For $C_{15}H_{21}O_2S$: C, 70.29; H, 4.72. Found: C, 70.56; H, 4.88.

Part B. 2-Iodobenzo[*b*]thiophen-3-yl 4-Methoxyphenyl Ether.

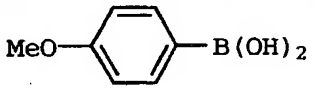


A solution of 133 mg (0.52 mmol) of 3-(4-methoxy-phenoxy)benzo[*b*]thiophene (Part A) in 3 mL of THF was treated with 0.33 mL of 1.6 M *n*-BuLi in hexanes (0.54 mmol) at -78 °C for 15 min and then treated with 138 mg (0.54 mmol) of I_2 in 3 mL of THF. The reaction was allowed to gradually warm to room temperature and then partitioned between brine and EtOAc/hexanes. The two phases were separated, the organic phase was washed with H_2O, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was crystallized from hexanes to

afford 143 mg (0.37 mmol; 72%) of the title compound as a solid.

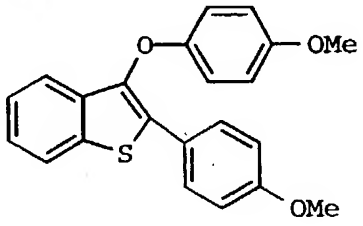
Anal. Calcd For $C_{15}H_{20}IO_2S$: C, 47.14; H, 2.90. Found: C, 47.21; H, 2.98.

Part C. (4-Methoxyphenyl)boronic Acid.



By essentially following the procedure detailed in Example 1, Part A, the title compound was prepared from 4-iodoanisole.

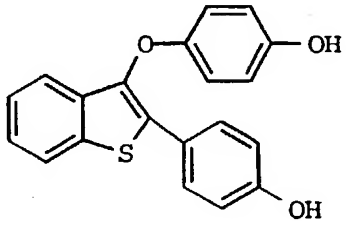
Part D. 2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl 4-Methoxyphenyl Ether.



By essentially following the procedure detailed in Example 1, Part B, the title compound was prepared from 2-iodo-3-(4-methoxyphenoxy)benzo[*b*]thiophene (Part B) and (4-methoxyphenyl)boronic acid (Part C) in 70% yield following chromatography (SiO_2; 5% EtOAc in hexanes).

Anal. Calcd For $C_{22}H_{18}O_3S$: C, 72.90; H, 5.01. Found: C, 72.82; H, 5.12.

Part E. 4-[[2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl]oxy]phenol.



By essentially following the procedure detailed in Example 5, Part B, the title compound was prepared from 2-(4-methoxyphenyl)-3-(4-methoxyphenoxy)benzo[*b*]thiophene (Part D) in 87% yield following radial chromatography (SiO_2; 25% EtOAc in hexanes).

FDMS 334 (M^+, 100); Anal. Calcd For $C_{20}H_{14}O_3S$: C, 71.84; H, 4.22. Found: C, 71.94; H, 4.35.

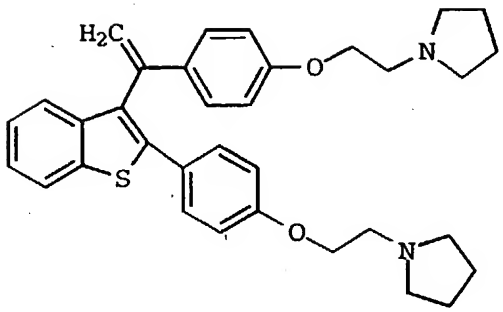
Part F. 1-[2-[4-[3-[4-[2-(1-Pyrrolidinyl)ethoxy]-phenoxy]benzo[*b*]thiophen-2-yl]phenoxy]ethyl]-pyrrolidine Dioxalate.

By essentially following the procedure detailed in Example 3, Part D the free base of the title compound was prepared from 4-[[2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl]oxy]phenol (Part E) and 1-(2-chloroethyl)pyrrolidine hydrochloride in 52% yield following radial chromatography (SiO_2; gradient of 2-10% MeOH in CH_2Cl_2). The free base was converted to the dioxalate salt according to the conditions described in Example 1, Part C.

^1H NMR (DMSO-d_6) δ 7.96 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.40-7.23 (m, 3H), 7.04 (d, J = 8.5 Hz, 2H), 6.91-6.80 (m, 4H), 4.38-4.13 (m, 4H), 3.55-3.41 (m, 4H), 3.36-3.14 (m, 8H), 1.97-1.78 (m, 8H); FDMS 529 (M+1; 100); Anal. Calcd For $C_{32}H_{36}N_2O_3S \cdot 2C_2H_2O_4$: C, 61.00; H, 5.69; N, 3.95. Found: C, 61.06; H, 5.86; N, 4.17.

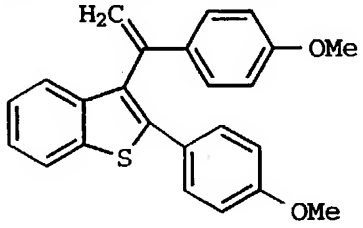
Example 12

Preparation of 1-[2-[4-[1-[2-[4-[2-(1-Pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl]ethenyl]phenoxy]-ethyl]pyrrolidine Dioxalate.



2 $C_2H_2O_4$

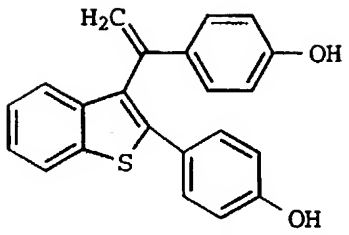
Part A. Methyl 4-[1-[2-(4-Methoxyphenyl)benzo[*b*]-thiophen-3-yl]ethenyl]phenyl Ether.



A solution of 1.20 g (3.36 mmol) of methyltriphenylphosphonium bromide in 50 mL of THF was treated with 0.45 g (4.01 mmol) of potassium *tert*-butoxide and the mixture stirred at room temperature for 0.5 h. To this was added dropwise 0.80 g (2.14 mmol) of 2-(4-methoxyphenyl)benzo[*b*]-thiophen-3-yl 4-methoxyphenyl ketone (Example 3, Part B) in 10 mL of THF and the reaction was stirred at room temperature for 18 h and then heated at gentle reflux for 48 h. The reaction was quenched by 100 mL of brine. The two layers were separated and the organic layer was dried over Na_2SO_4. Concentration *in vacuo* gave 1.36 g of an oil which was purified by radial chromatography (SiO_2; 10% EtOAc in hexanes) to afford 0.610 g (1.64 mmol; 77%) of the desired product as an oil.

FDMS 372 (M^+; 100).

Part B. 4-[1-[2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl]ethenyl]phenol.



By essentially following the procedure detailed in Example 5, Part B, the title compound was prepared from methyl 4-[1-[2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl]-ethenyl]phenyl ether (Part A) in 67% yield as a yellow solid following radial chromatography (SiO_2; gradient of 20-40% EtOAc in hexanes).
FDMS 344 (M^+; 100).

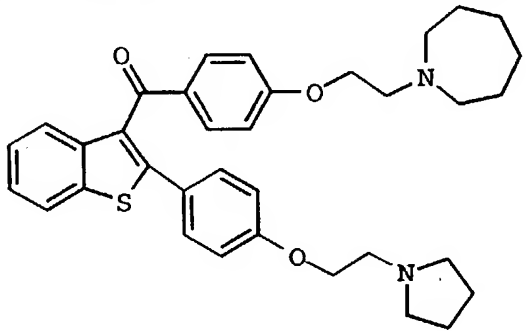
Part C. 1-[2-[4-[1-[2-[4-[2-(1-Pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl]ethenyl]phenoxy]ethyl]-pyrrolidine Dioxalate.

By essentially following the procedure detailed in Example 3, Part D, the free base of the title compound was prepared from 4-[1-[2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl]ethenyl]phenol (Part B) and 1-(2-chloroethyl)pyrrolidine hydrochloride in 67% yield as an oil following radial chromatography (SiO_2; gradient of 2-10% MeOH in CH_2Cl_2). The free base was converted to the dioxalate salt according to the conditions described in Example 1, Part C.

^1H NMR (DMSO-d_6) δ 7.95 (d, J = 7.5 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.38-7.16 (m, 5H), 6.95 (d, J = 8.1 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 5.99 (s, 1H), 5.14 (s, 1H), 4.32-4.10 (m, 4H), 3.54-3.36 (m, 4H), 3.29-3.12 (m, 8H), 1.98-1.72 (m, 8H); FDMS 539 (M+1; 100); Anal. Calcd For $C_{34}H_{38}N_2O_2S \cdot 2C_2H_2O_4$: C, 63.49; H, 5.89: N, 3.90. Found: C, 63.78; H, 6.14; N, 4.10.

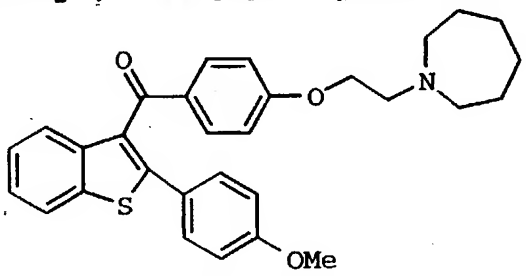
Example 13

Preparation of 4-[2-(Hexahydro-1H-azepin-1-yl)ethoxy]-phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl Ketone Dioxalate.



2 $C_2H_2O_4$

Part A. 4-[2-(Hexahydro-1H-azepin-1-yl)ethoxy]phenyl 2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl Ketone.



By essentially following the procedure detailed in Example 1, Part C, the title compound was prepared from 2-(4-methoxyphenyl)benzo[*b*]thiophene (Example 3; Part A) and 4-[2-(hexahydro-1H-azepin-1-yl)ethoxy]benzoic acid hydrochloride in 35% yield as an oil following radial chromatography (SiO_2; gradient of 1-10% isopropanol in CH_2Cl_2).

FDMS 485 (M^+; 100).

Part B. 4-[2-(Hexahydro-1H-azepin-1-yl)ethoxy]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.

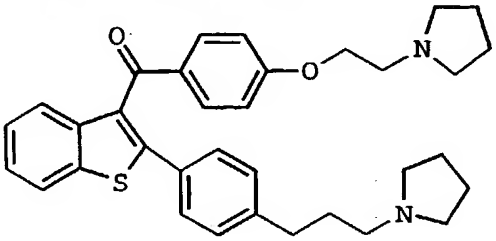
Deprotection of the 4-[2-(hexahydro-1H-azepin-1-yl)-ethoxy]phenyl] 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl ketone (Part A) was effected according to the conditions described in Example 1, Part D. The resulting phenol was

alkylated with 1-(2-chloroethyl)pyrrolidine hydrochloride according to the procedure detailed in Example 3, Part D to afford the free base of title compound which was converted to the dioxalate salt according to the methods described in Example 1, Part C.

FDMS 569 (M^+; 100); Anal. Calcd For $C_{35}H_{38}N_2O_3S \cdot 2C_2H_2O_4 \cdot H_2O$: C, 60.37; H, 6.10; N, 3.61. Found: C, 60.05; H, 5.71; N, 3.84; HRMS Calcd for $C_{35}H_{40}N_2O_3S$: 568.2838. Found: 568.2869.

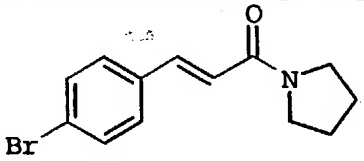
Example 14

Preparation of 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl 2-[4-[3-(1-Pyrrolidinyl)propyl]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.



2 $C_2H_2O_4$

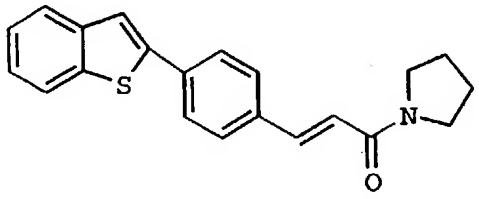
Part A. 1-(*trans*-4-Bromocinnamoyl)pyrrolidine.



A mixture of 5.0 g (22.0 mmol) of 4-bromocinnamic acid, 6 mL of oxalyl chloride and 3 drops of DMF in 40 mL of CH_2Cl_2 was heated to gentle reflux until gas evolution ceased. The volatiles were removed *in vacuo* and the residue was taken up in 50 mL of CH_2Cl_2. Pyrrolidine (10 mL; 120 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was evaporated *in vacuo* and chromatographed to afford 5.36 g (19.1 mmol; 87%) of the title compound.

FDMS 279 (M-1), 281 (M+1); Anal. Calcd For $C_{13}H_{14}BrNO$: C, 55.73; H, 5.04; N, 5.00. Found: C, 56.00; H, 5.06; N, 5.04.

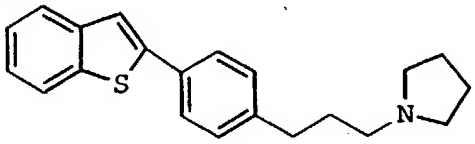
Part B. 1-[*trans*-4-(Benzo[*b*]thiophen-2-yl)cinnamoyl]-pyrrolidine.



By essentially following the procedure detailed in Example 1, Part B, the title compound was prepared from benzo[*b*]thiophene-2-boronic acid and 1-(*trans*-4-bromocinnamoyl)pyrrolidine (Part A) in 43% yield following chromatography.

FDMS 333 (M^+), 334 (M+1).

Part C. 1-[3-[4-(Benzo[*b*]thiophen-2-yl)phenyl]-propyl]pyrrolidine.



A solution of 1.2 g (3.6 mmol) of 1-[*trans*-4-(benzo[*b*]thiophen-2-yl)cinnamoyl]pyrrolidine (Part B) in 15 mL of THF was treated with 75 mg (2.0 mmol) of $LiAlH_4$ at -15 °C. After complete consumption of starting material, the reaction was cautiously quenched with H_2O. The mixture was extracted with EtOAc and the combined organic layers were evaporated *in vacuo*. Chromatography afforded 600 mg (1.9 mmol; 52% yield) of the desired product.
FDMS 320 (M-1).

Part D. 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl 2-[4-[3-(1-Pyrrolidinyl)propyl]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.

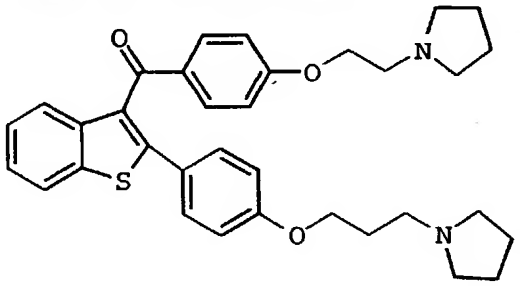
By essentially following the procedure outlined in Example 1, Part C, the free base of the title compound was

prepared from 1-[3-[4-(benzo[*b*]thiophen-2-yl)phenyl]propyl]-pyrrolidine (Part C) and 4-[2-(1-pyrrolidinyl)ethoxy]benzoic acid hydrochloride in 11% yield. Conversion to the dioxalate salt followed from the procedure described in Example 1, Part C.

mp 105 - 112 °C; FDMS 536 (M+1; 100); Anal. Calcd For $C_{32}H_{38}N_2O_2S \cdot 3C_2H_2O_4$: C, 58.16; H, 5.65; N, 3.57. Found: C, 58.06; H, 5.15; N, 3.93.

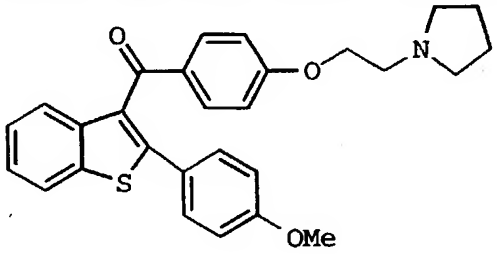
Example 15

Preparation of 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl 2-[4-[3-(1-Pyrrolidinyl)propoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.



2 $C_2H_2O_4$

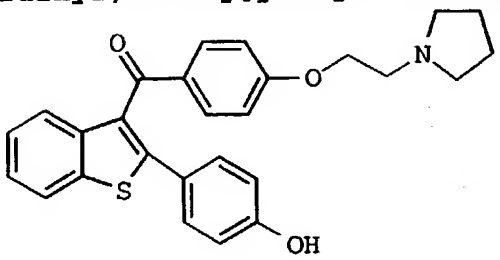
Part A. 2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl Ketone.



By essentially following the procedure detailed in Example 1, Part C, the title compound was prepared from 2-(4-methoxyphenyl)benzo[*b*]thiophene (Example 3, Part A) and 4-[2-(1-pyrrolidinyl)ethoxy]benzoic acid hydrochloride in 59% yield as an oil following radial chromatography (SiO_2; gradient of 2-5% MeOH in CH_2Cl_2).

Part B. 2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl

4-[2-(1-Pyrrolidinyl)ethoxy]phenyl Ketone.



By essentially following the procedure detailed in Example 1, Part D, the title compound was prepared from 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl 4-[2-(1-pyrrolidinyl)-ethoxy]phenyl ketone (Part A) in 33% yield as an oil following radial chromatography (SiO_2; gradient of 2-10% MeOH in CH_2Cl_2).

FDMS 443 (M^+; 100); Anal. Calcd For $C_{27}H_{25}NO_3S$: C, 73.11; H, 5.68; N, 3.16. Found: C, 73.11; H, 5.89; N, 3.20.

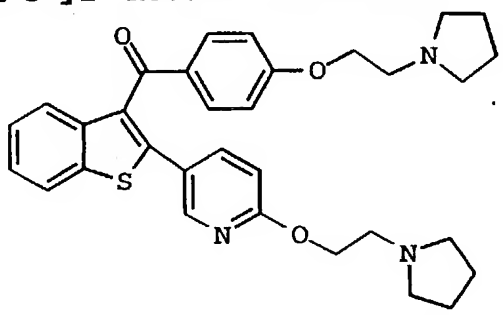
Part C. 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl 2-[4-[3-(1-Pyrrolidinyl)propoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.

By essentially following the procedure detailed in Example 3, Part D, the free base of the title compound was prepared from 2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl 4-[2-(1-pyrrolidinyl)ethoxy]phenyl ketone (Part B) and 1-(2-chloroethyl)pyrrolidine hydrochloride in 69% yield following radial chromatography (SiO_2; gradient of 5-10% MeOH in CH_2Cl_2). The product was converted to the dioxalate salt according to the conditions of Example 1, Part C.

^1H NMR (DMSO-d_6) δ 8.04 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 8.7 Hz, 2H), 7.42-7.29 (m, 5H), 6.95 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.6 Hz, 2H), 4.35-4.23 (m, 2H), 3.98 (t, J = 5.5 Hz, 2H), 3.58-3.42 (m, 2H), 3.34-3.09 (m, 10H), 2.13-1.99 (m, 2H), 1.95-1.76 (m, 8H); FDMS 555 (M+1; 100); Anal. Calcd For $C_{34}H_{38}N_2O_3S \cdot 2C_2H_2O_4 \cdot 1.5H_2O$: C, 59.91; H, 5.95; N, 3.68. Found: C, 59.72; H, 5.70; N, 3.48.

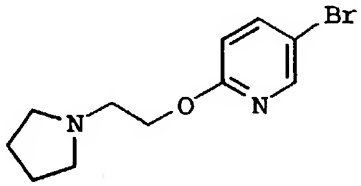
Example 16

Preparation of 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl 2-[6-[2-(1-Pyrrolidinyl)ethoxy]pyrid-3-yl]benzo[*b*]-thiophen-3-yl Ketone Dioxalate.



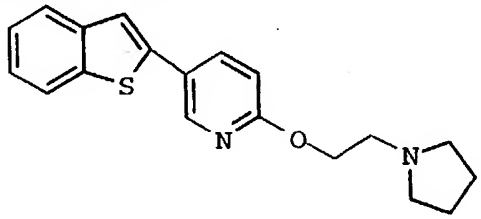
2 $C_2H_2O_4$

Part A. 5-Bromopyrid-2-yl 2-(1-Pyrrolidinyl)ethyl Ether.



A solution of 8.00 g (69.6 mmol) of N-(2-hydroxyethyl)-pyrrolidine in 150 mL of xylenes was treated with 534 mg (23.2 mmol) of Na and the mixture was heated to 80 °C until all the Na had disappeared. The reaction was cooled to 23 °C and 5.50 g (23.2 mmol) of 2,5-dibromopyridine was added. The mixture was stirred at room temperature for 2.25 h and was concentrated *in vacuo*. Purification by flash chromatography (SiO_2; gradient of 50-70% EtOAc in hexanes) afforded 3.53 g (13.0 mmol; 56%) of the title compound.

Part B. 5-(Benzo[*b*]thiophen-2-yl)pyrid-2-yl 2-(1-Pyrrolidinyl)ethyl Ether.



By essentially following the procedure detailed in Example 1, Part B, the title compound was prepared from

benzo[*b*]thiophene-2-boronic acid and 5-bromopyrid-2-yl 2-(1-pyrrolidinyl)ethyl ether (Part A) in 68% yield as an oil following flash chromatography (SiO_2; gradient of 0-4% MeOH in $CHCl_3$).

FDMS 324 (M^+; 100).

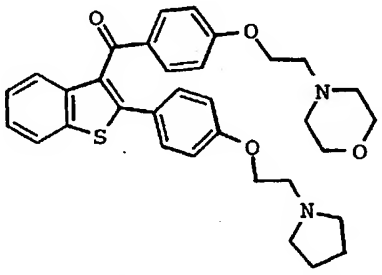
Part C. 4-[2-(1-Pyrrolidinyl)ethoxy]phenyl 2-[6-[2-(1-Pyrrolidinyl)ethoxy]pyrid-3-yl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.

By essentially following the procedure detailed in Example 1, Part C, the title compound was prepared from 5-(benzo[*b*]thiophen-2-yl)pyrid-2-yl 2-(1-pyrrolidinyl)ethyl ether (Part B) and 4-[2-(1-pyrrolidinyl)-ethoxy]benzoic acid hydrochloride in 30% yield as a solid following flash chromatography (SiO_2; 5% MeOH in $CHCl_3$). The free base was converted to the dioxalate salt according to the conditions outlined in Example 1, Part C.

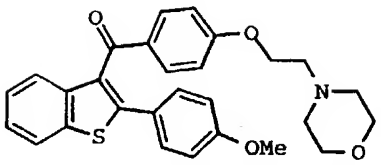
FDMS 543 (M+2; 100); Anal. Calcd For $C_{32}H_{35}N_3O_3S \cdot 2C_2H_2O_4$: C, 59.91; H, 5.45; N, 5.82. Found: C, 59.80; H, 5.67; N, 5.61.

Example 17

Preparation of 4-[2-(4-Morpholinyl)ethoxy]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.



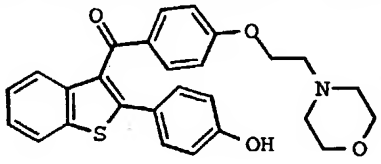
Part A. 2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl 4-[2-(4-Morpholinyl)ethoxy]phenyl Ketone.



By essentially following the procedure outlined in Example 3, part D, the title compound was prepared in 96% yield from 4-hydroxyphenyl 2-(4-methoxyphenyl)benzo[*b*]-thiophen-3-yl ketone (Example 28, Part A) to yield an off-white foam following column chromatography (SiO_2; gradient 0-5% MeOH in EtOAc).

^1H NMR ($CDCl_3$) δ 7.86-7.83 (m, 1H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.65-7.62 (m, 1H), 7.39-7.32 (m, 4H), 6.76 (d, *J* = 8.8 Hz, 4H), 4.08 (t, *J* = 5.6 Hz, 2H), 3.75 (s, 3H), 3.71 (t, *J* = 4.7 Hz, 4H), 2.77 (t, *J* = 5.6 Hz, 2H), 2.54 (t, *J* = 4.5 Hz, 4H).

Part B. 2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl 4-[2-(4-Morpholinyl)ethoxy]phenyl Ketone.



Following the procedure outlined in Example 1, part D, the title compound was prepared in 91% yield from 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl 4-[2-(4-morpholinyl)-ethoxy]phenyl ketone (Part A). The desired compound was isolated as a white solid after flash chromatography (SiO_2; gradient 0-10% MeOH in EtOAc) and recrystallization from THF-hexanes.

mp 188-189 °C; IR (KBr) 1598 cm^{-1}; FDMS 459 (M^+); Anal. Calcd for $C_{27}H_{25}NO_4S$: C, 70.57; H, 5.48; N, 3.05. Found C, 70.58; H, 5.57; N, 3.35.

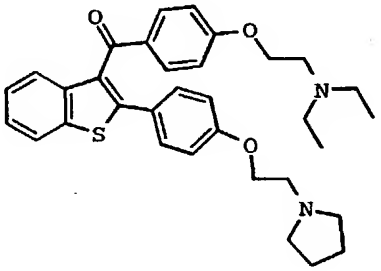
Part C. 4-[2-(4-Morpholinyl)ethoxy]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.

Following Example 3, part D, the title compound was prepared from 2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl 4-[2-(4-morpholinyl)ethoxy]phenyl ketone (Part B) in 78% yield as a light oil after flash chromatography [SiO_2; gradient 0-12% (1:2 TEA-*i*-PrOH) in THF]. Conversion to the dioxalate salt was carried out as detailed in Example 1, part C.

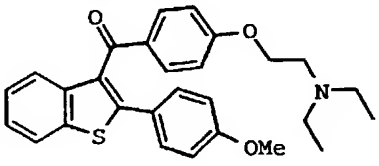
mp 73 °C; IR (KBr) 1598 cm^{-1}; ^1H NMR (CD_3OD) δ 7.93 (d, *J* = 7.1 Hz, 1H), 7.71 (d, *J* = 8.8 Hz, 2H:), 7.56 (d, *J* = 7.1 Hz, 1H), 7.36 (d, *J* = 8.7 Hz, 4H), 6.88 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.36 (distorted t, 2H), 4.25 (distorted t, *J* = 4.8 Hz, 2H), 3.90 (br t, *J* = 4.6 Hz, 4H), 3.61-3.28 (m, 12 H), 2.06 (m, 4H); FDMS 557 (M+1); Anal. Calcd for $C_{35}H_{38}N_2O_8S \cdot 2C_2H_2O_4 \cdot 2H_2O$: C, 57.50; H, 5.74; N, 3.62. Found: C, 57.39; H, 5.56; N, 3.70.

Example 18

Preparation of 4-[2-(Diethylamino)ethoxy]phenyl 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.



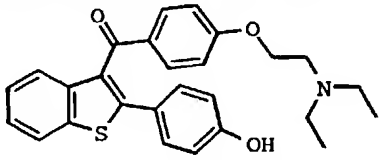
Part A. 4-[2-(Diethylamino)ethoxy]phenyl 2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl Ketone.



By essentially following the procedure outlined in Example 3, part D, the title compound was prepared from 4-hydroxyphenyl 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl ketone (Example 28, Part A) and 2-diethylaminoethyl chloride in 86% yield. Flash chromatography [SiO_2; gradient 1-4% of (1:1 TEA-MeOH) in EtOAc] gave the desired compound as a light oil.

IR ($CHCl_3$) 1598 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86-7.84 (m, 1H), 7.83-7.75 (m, 2H), 7.65-7.62 (m, 1H), 7.39-7.25 (m, 4H), 6.76 (d, J = 8.5 Hz, 4H), 4.03 (t, J = 6.0 Hz, 2H), 3.75 (s, 3H), 2.84 (t, J = 6.0 Hz, 2H), 2.66-2.59 (m, 4H), 1.05 (t, J = 7.1 Hz, 6H); FDMS 459 (M^+); Anal. Calcd for $C_{28}H_{29}NO_3S$: C, 73.17; H, 6.36; N, 3.05. Found: C, 73.11; H, 6.49; N, 3.17.

Part B. 4-[2-(Diethylamino)ethoxy]phenyl 2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl Ketone.



By essentially following the procedure outlined in Example 1, part D, the title compound was prepared in 71% yield from 4-[2-(diethylamino)ethoxy]phenyl 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl ketone (Part A) as an orange foam following flash chromatography (SiO_2; 5% TEA in THF).

^1H NMR ($CDCl_3$) δ 7.89-7.86 (m, 1H), 7.76 (d, J = 8.7 Hz, 2H), 7.72-7.69 (m, 1H), 7.39-7.36 (m, 2H), 7.25 (d, J = 8.4 Hz, 2H), 6.95 (br s, 1H), 6.72 (d, J = 8.7 Hz, 2H), 6.64 (d, J = 8.4 Hz, 2H), 4.07 (t, J = 5.8 Hz, 2H), 2.91 (t, J = 5.9 Hz, 2H), 2.70 (q, J = 7.1 Hz, 4H), 1.09 (t. J = 7.1 Hz, 6H).

Part C. 4-[2-(Diethylamino)ethoxy]phenyl 2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone Dioxalate.

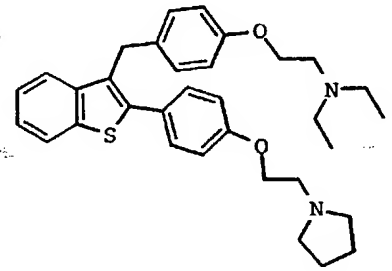
By essentially following the procedure outlined in Example 3, part D, the title compound was prepared from 4-[2-

(diethylamino)ethoxy]phenyl 2-(4-hydroxyphenyl)benzo[*b*]-thiophen-3-yl ketone (Part B) in 95% yield following flash chromatography (SiO_2; gradient 60% THF containing 3% TEA to 80% THF in hexanes) as a tan solid. Conversion to the dioxalate salt was carried out in 94% yield as detailed in Example 1, part C.

mp 176-179 °C; ^{1}H NMR (CD_3OD) δ 7.92 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.74 (d, *J* = 8.9 Hz, 2H), 7.54 (dd, *J* = 7,2, 1.7 Hz, 1H), 7.41-7.34 (m, 4H), 6.92 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 4.36 (distorted t, 2H), 4.27 (distorted t, 2H), 3.59 (m 4H), 3.28 (m, 8H), 2.08 (br s, 4H), 1.31 (t, *J* = 7.2 Hz, 6H); FDMS 543 (M+1), 634 (M+2+$C_2H_2O_4$).

Example 19

Preparation of 1-[2-[4-[3-[4-[2-(Diethylamino)ethoxy]-benzyl]benzo[*b*]thiophen-2-yl]phenoxy]ethyl]pyrrolidine Dioxalate.



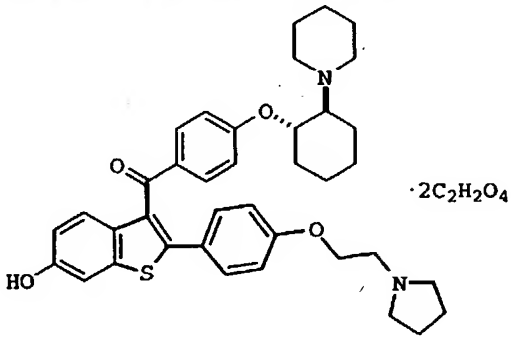
By essentially following the procedure outlined in Example 2, part D, the title compound was prepared in 91% yield from 4-[2-(diethylamino)ethoxy]phenyl 2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl ketone (Part C). Flash chromatography [SiO_2; 80% THF in hexanes with 3% TEA (v/v)] gave a white gummy solid which was converted to the dioxalate salt following the method described in Example 1, part C.

^{1}H NMR (DMSO-d_6) δ 7.99 (m, 1H), 7.59 (br d, *J* = 6.3 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.36 (m, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H),

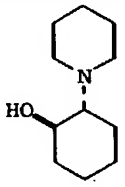
4.38 (br s, 2H), 4.27 (br. s, 2H), 4.22 (br s, 2H), 3.57 (br s, 2H), 3.44 (br s, 2H), 3.35 (br. s, 4H), 3.16 (dt, J = 7.1, 6.7 Hz, 4H), 1.96 (br s, 4H), 1.21 (t, J = 6.9 Hz, 6H); FDMS 529 (M+1; Anal. Calcd for $C_{33}H_{40}N_2O_2S \cdot 2C_2H_2O_4 \cdot H_2O$: C, 61.14; H, 6.38; N, 3.85. Found: C, 61.04; H, 6.32; N, 3.61.

Example 20

Preparation of (±)-6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-Piperidyl)cyclohexyl]oxy]phenyl Ketone Dioxalate.



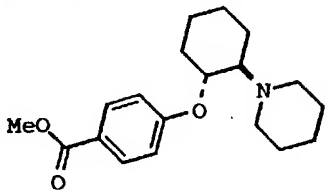
Part A. (±)-*trans*-(1-Piperidyl)cyclohexan-2-ol.



To a solution of 41.63 g (0.30 mol) of K_2CO_3 in ca. 200 mL of H_2O was added 12.16 g (0.10 mol) of piperidine hydrochloride at 0 °C, followed by 10.1 mL (0.10 mol) of cyclohexene oxide. After 5 min at 0 °C, the ice bath was removed and the cloudy solution was stirred at room temperature overnight (18 h). The mixture was then extracted with EtOAc (3 x 500 mL) which was washed with 200 mL of H_2O and 200 mL of brine. The combined extracts were dried over $MgSO_4$, concentrated, and dried under vacuum to afford 3.64 g (20%) of the crude amine which was used without further purification for the following reaction.

IR (KBr) 3435 cm^{-1}; FDMS 184 (M+1), 229 (100).

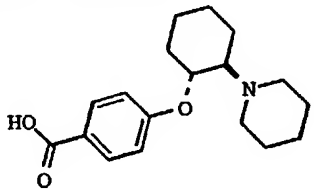
Part B. Methyl (±)-4-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]benzoate.



To a solution of methyl 4-hydroxybenzoate (1.476 g, 9.70 mmol) in 175 mL of anhydrous THF was added 3.557 g (19.4 mmol) of *trans*-(1-piperidyl)cyclohexan-2-ol, (Part A), 5.090 g (19.4 mmol) of triphenylphosphine and 3.10 mL (19.4 mmol) of diethyl azodicarboxylate at room temperature. The reaction mixture was stirred for 3 days and then concentrated under reduced pressure. The residue was purified by PrepLC (2.5 to 4% of (10% concd NH_4OH in MeOH) in CH_2Cl_2) to afford 2.232 g (7.03 mmol, 73%) of an orange solid.

mp 88-91 °C; ^1H NMR ($CDCl_3$) δ 7.97 (d, J = 8.8 Hz, 2H), 6.92 (d J = 8.9 Hz, 2H), 4.32 (td, J = 9.8, 4.2 Hz, 1H), 3.88 (s, 3H), 2.80-2.47 (m, 5H), 2.23-2.15 (m, 1H), 2.07-1.92 (m, 1H), 1.76 (m, 2H), 1.57-1.20 (m, 10H); FDMS 317 (M^+).

Part C. (±)-4-[[*trans*-2-(1-Piperidyl)-cyclohexyl]oxy]benzoic Acid.

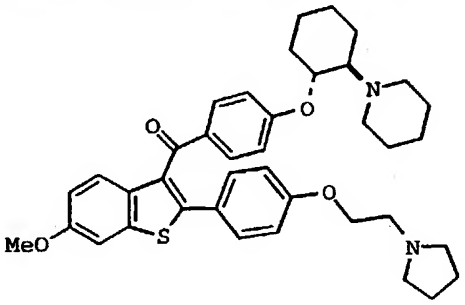


A solution of methyl 4-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]benzoate (Part B) (2.232 g, 7.03 mmol) and 10.6 mL (10.6 mmol) of 1.0 N NaOH in 60 mL of 1:1 mixture of MeOH/THF was stirred at 80 °C for 20 h. The mixture was then cooled to room temperature, stirred for additional 7 h, and concentrated under reduced pressure. The residue was dissolved in 50 mL of 1.0 N HCl. This solution was extracted with 200 mL of EtOAc. The organic layer was washed with 200 mL of water. The combined aqueous layers were cooled to 0 °C

and neutralized with 15 mL of 2.0 N NaOH. They were then concentrated under reduced pressure and the residue was taken up in 10% MeOH in CH_2Cl_2 and then filtered. The filtrate was concentrated and the residue was dried over P_2O_5 in a vacuum oven at 55 °C.

mp 264-266 °C (dec); ^{1}H NMR (DMSO-d_6) δ 7.79 (d, J = 7.7 Hz, 2H), 6.87 (d, J = 8.1 Hz, 2H), 4.40 (m, 1H), 2.65-2.55 (m, 4H), 2.07 (m, 1H), 1.77-1.58 (m, 3H), 1.40-1.15 (m, 11H); FDMS 304 (M+1), 482 (base); Anal. Calcd for $C_{18}H_{25}NO_3 \cdot 0.73NaCl$: C, 62.47, H, 7.28, N, 4.05. Found: C, 62.92, H, 7.47, N, 4.15.

Part D. (±)-6-Methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-Piperidyl)cyclohexyl]oxy]phenyl Ketone.



1.698 g (5.60 mmol) of 4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]benzoic acid (Part C) was dissolved in 30 mL of thionyl chloride at room temperature. To this was added 434 µL (5.60 mmol) of DMF as a catalyst. The mixture was stirred for 3 days at room temperature. The thionyl chloride was removed under reduced pressure and the residue was treated with dry benzene to remove azeotropically the residual thionyl chloride and then placed under high vacuum. The crude acid chloride was suspended in 50 mL of anhydrous dichloroethane, and to this was added 1.799 g (5.09 mmol) of 6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]-thiophene (Example 1, Part B). After cooling the slurry to 0 °C, aluminum bromide (6.79 g, 25.4 mmol) was added, producing

a dark red mixture. The ice bath was removed and the reaction mixture was stirred at room temperature for 6 h. The mixture was poured into 100 mL of cooled (0 °C) 2.0 N NaOH. The aqueous layer was extracted with EtOAc (3 x 400 mL). The combined organic layers were washed with 300 mL of brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified using PrepLC (8% of (10% concd NH_4OH in MeOH) in CH_2Cl_2).

mp 68-72 °C; ^1H NMR ($CDCl_3$) δ 7.76 (d, *J* = 8.9 Hz, 2H), 7.49 (d, *J* = 8.9 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 2.4 Hz, 1H), 6.94 (dd, *J* = 8.9 and 2.4 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 4H), 4.26 (td, *J* = 9.8, 4.1 Hz, 1H), 4.09 (t, *J* = 5.8 Hz, 2H), 3.88 (s, 3H), 2.92 (t, *J* = 5.8 Hz, 2H), 2.69 (m, 7H), 2.50 (m, 2H), 2.17-1.95 (m, 2H), 1.84 (m, 4H), 1.73 (m, 2H), 1.50-1.15 (m, 10H); FDMS 639 (M^+); Anal. Calcd for $C_{39}H_{46}N_2O_4S$: C, 73.32; H, 7.26; N, 4.38. Found: C, 73.03; H, 7.13; N, 4.29.

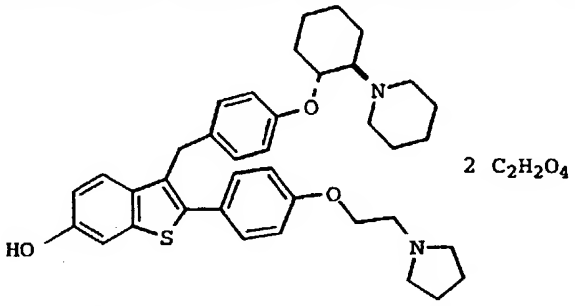
Part E. (±)-6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-Piperidyl)cyclohexyl]oxy]phenyl Ketone Dioxalate.

The title compound was prepared from (±)-6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]phenyl ketone (Part D) as a yellow solid by essentially following the procedures described in Example 21, Parts B and C.

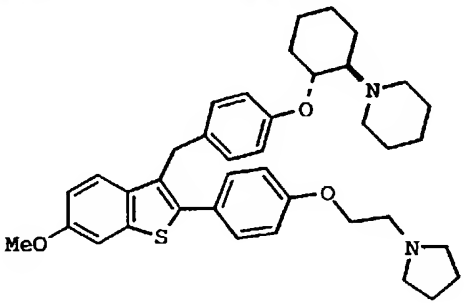
mp 140-145° C; ^1H NMR (DMSO-d_6) δ 7.70 (d, *J* = 8.6 Hz, 2H), 7.38 (d, *J* = 2.2 Hz, 1H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 1H), 7.06 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 10.9 Hz, 1H), 4.69 (m, 1H), 4.25 (m, 2H), 3.50 (m, 2H), 3.28 (m, 5H), 3.09 (m, 2H), 2.93 (m, 2H), 2.07 (m, 2H), 1.91 (m, 4H), 1.80 - 1.20 (m, 12H); FDMS 624 (M^+); Anal. Calcd for $C_{38}H_{44}N_2O_4S \cdot 2.87C_2H_2O_4$: C, 59.48; H, 5.68; N, 3.17. Found: C, 59.45; H, 5.85; N, 3.35.

Example 21

Preparation of (±)-6-Hydroxy-3-[4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



Part A. (±)-6-Methoxy-3-[4-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene.

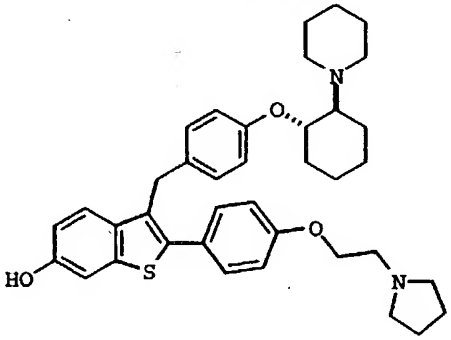


To a solution of 6-methoxy-[2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl] 4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]phenyl ketone (Example 20, Part D) (1.340 g, 2.10 mmol) in 21.0 mL of anhydrous THF was added dropwise 2.10 mL (2.10 mmol) of 1.0 M $LiAlH_4$ in THF at 0 °C. The reaction mixture was stirred for 1 h and 45 min while allowing the temperature to be raised to 20 °C. The reaction was then quenched at 0 °C by addition of 80 µL of H_2O, followed by 80 µL of 15% NaOH, and then an additional 240 µL of H_2O (Fieser workup). This mixture was then filtered over a pad of silica gel and washed with THF. The filtrate was concentrated to dryness under reduced pressure. The crude alcohol was dissolved in 21.0 mL of anhydrous CH_2Cl_2 and cooled to 0 °C. To this was added 2.30 mL (14.7 mmol) of triethylsilane, and the reaction mixture was stirred for 5

min, followed by a dropwise addition of 1.60 mL (21.0 mmol) of trifluoroacetic acid. The ice bath was removed and the reaction mixture was stirred further for 3 h 45 min before being quenched with 25.0 mL of saturated $NaHCO_3$ at 0 °C. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic layers were dried over $MgSO_4$, concentrated under reduced pressure, and purified by flash chromatography (silica gel, 57:40:3 hexanes-THF-TEA) to afford 1.251 g (2.00 mmol, 96%) of a clear gel.

^1H NMR: ($CDCl_3$) δ 7.41 (d, *J* = 8.9 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.31 (d, *J* = 2.3 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.93 (m, 1H), 6.81 (d, *J* = 8.6 Hz, 2H), 4.15 (m, 5H), 3.86 (s, 3H), 2.94 (t, *J* = 5.9 Hz, 2H), 2.85-2.55 (m, 9H), 2.20-2.10 (m, 2H), 1.83 (m, 4H), 1.72 (m, 2H) 1.58-1.48 (m, 4H), 1.42-1.18 (m, 6H); FDMS 625 (M+); Anal. Calcd for $C_{39}H_{48}N_2O_3S$: C, 74.96; H, 7.74; N, 4.48. Found: C, 75.00; H, 7.94; N, 4.35.

Part B. (±)-6-Hydroxy-3-[4-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene.



To a solution of 1.150 g (1.84 mmol) (±)-6-methoxy-3-[4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene (Part A) in 20.0 mL of anhydrous dichloroethane at 0 °C was added 1.10 mL (14.7 mmol) of ethanethiol, followed by the addition of aluminum chloride (982 mg, 7.36 mmol). The yellow biphasic

reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched at 0 °C with 20 mL of saturated aqueous $NaHCO_3$. The aqueous layer was separated and extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with 150 mL of brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by using flash chromatography (silica gel, 60:37:3 THF-hexanes-TEA) to afford 1.067 g (1.75 mmol, 95%) of a white solid.

mp 179-182 °C; ^1H NMR ($CDCl_3$) δ 7.30 (dd, J = 8.7, 1.9 Hz, 2H), 7.07 (d, J = 2.2 Hz, 1H), 7.01 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 2.2 Hz, 1H), 6.77 (m, 5H), 4.14 (t, J = 5.6 Hz, 2H), 4.12 (buried m, 1H), 4.10 (s, 2H), 3.00 (t, J = 5.5 Hz, 2H), 2.81 (m, 5H), 2.69 (m, 4H), 2.14 (m, 2H), 1.87 (m, 4H), 1.71 (m, 2H), 1.58 (m, 3H), 1.38 (m, 3H), 1.26 (m, 4H); FDMS 611 (M^+); Anal. Calcd for $C_{38}H_{46}N_2O_3S$: C, 74.71; H, 7.59; N, 4.59. Found: C, 74.92; H, 7.80; N, 4.53.

Part C. (±)-6-Hydroxy-3-[4-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

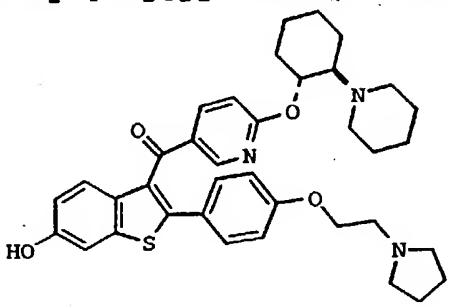
In approximately 4 mL of $CHCl_3$-EtOAc (1:1) was dissolved 14.7 mg (0.164 mmol) of oxalic acid. To this was added dropwise 50.0 mg (0.082 mmol) of (±)-6-hydroxy-3-[4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene (Part C) in 7 mL of $CHCl_3$. A white precipitate was formed, and the slurry was sonicated for 30 min and filtered with EtOAc rinse. The precipitate was dried over P_2O_5 at 55 °C in a vacuum oven.

mp 163-165 °C; ^1H NMR (DMSO-d_6) δ 7.44 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.7 Hz, 1H), 7.27 (s, 1H), 7.09 (d, J = 8.6 Hz, 2H), 7.04 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.5 Hz, 2H), 6.81 (dd, J = 8.7, 2.1 Hz, 1H), 4.49 (m, 1H), 4.33 (br t, 2H), 4.12 (s, 2H), 3.51 (br t, 2H), 3.28 (m, 5H), 3.15 (m, 2H), 3.01 (m, 2H), 2.10 (m, 2H), 1.92 (m, 4H), 1.75-1.60 (m, 6H),

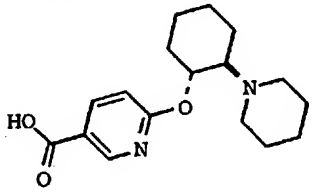
1.55-1.40 (m, 3H), 1.26 (m, 3H); FDMS 611 (M^+); Anal. Calcd for $C_{38}H_{46}N_2O_3S \cdot 2.0C_2H_2O_4 \cdot 0.24CHCl_3$: C, 61.90; H, 6.18; N, 3.42. Found: C, 61.90; H, 5.99; N, 3.37.

Example 22

Preparation of (±)-6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 6-[[*trans*-2-(1-Piperidyl)cyclohexyl]oxy]pyrid-3-yl Ketone.



Part A. (±)-6-[[*trans*-2-(1-Piperidyl)cyclohexyl]oxy]-3-pyridinecarboxylic Acid.



The title compound was prepared from methyl (±)-6-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]-3-pyridinecarboxylate as an off-white solid by essentially following the procedure described in Example 20, Part C.

^1H NMR (DMSO-d_6) δ 10.00 (m, 1H) 8.73 (dd, J = 2.4, 0.5 Hz, 1H), 8.21 (dd, J = 8.7, 2.4 Hz, 1H), 7.04 (d, J = 8.6 Hz, 1H), 5.35 (m, 1H), 3.60 (br t, 1H), 3.49 (br d, J = 11.6 Hz, 1H), 3.40 (br d, J = 11.4 Hz, 1H), 3.18 (br q, 1H), 2.73 (br q, J = 11.2 Hz, 1H), 2.48 (m, 1H), 2.23 (m, 1H), 2.10-1.83 (m, 2H), 1.83-1.58 (m, 6H), 1.45-1.12 (m, 4H).

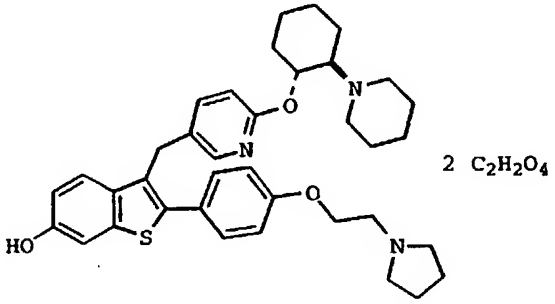
Part B. (±)-6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 6-[[*trans*-2-(1-Piperidyl)cyclohexyl]oxy]pyrid-3-yl Ketone.

The title compound was prepared in 29% yield from 6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]-thiophene (Example 1, Part B) and (±)-6-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]-3-pyridinecarboxylic acid (Part A) by essentially following the procedures detailed in Example 20, Parts D and E.

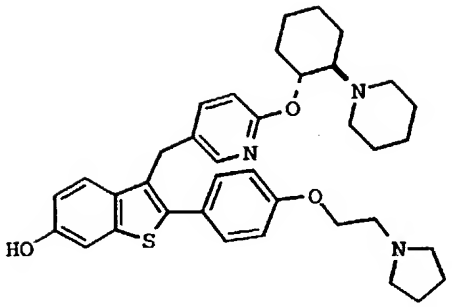
^{1}H NMR ($CDCl_3$) δ 8.32 (d, *J* = 2.4 Hz, 1H), 7.70 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.41 (d, *J* = 8.9 Hz, 1H), 7.30 (d, *J* = 2.1 Hz, 1H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.81 (dd, *J* = 8.8, 2.2 Hz, 1H), 6.62 (d, *J* = 8.6 Hz, 2H), 6.44 (d, *J* = 8.6 Hz, 1H), 5.22 (m, 1H), 4.07 (t, *J* = 5.4 Hz, 2H), 3.00 (t, *J* = 5.4 Hz, 2H), 2.87-2.57 (m, 9H), 2.20-2.00 (m, 2H), 1.95-1.65 (m, 6H), 1.60-1.20 (m, 10H); FDMS 626 (M^+); Anal. Calcd for $C_{37}H_{43}N_3O_4S \cdot 0.59H_2O$: C, 69.83; H, 7.00; N, 6.60. Found: C, 69.58; H, 6.73; N, 6.99.

Example 23

Preparation of (±)-6-Hydroxy-3-[6-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]pyrid-3-yl]methyl-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



Part A. (±)-6-Hydroxy-3-[6-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]pyrid-3-yl]methyl-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene.



The title compound was prepared in 39% yield from 6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]-thiophen-3-yl 6-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]pyrid-3-yl ketone (Example 22, Part B) by essentially following the procedures detailed in Example 21, Parts A and B.

mp 170-174 °C; ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 2.2 Hz, 1H), 7.31-7.21 (m, 4H), 7.03 (d, J = 2.1 Hz, 1H), 6.80 (d, J = 8.6 Hz, 3H), 6.54 (d, J = 8.5 Hz, 1H), 5.11 (m, 1H), 4.14 (t, J = 5.4 Hz, 2H), 4.05 (s, 2H), 2.99 (t, J = 5.4 Hz, 2H), 2.80 (m, 5H), 2.59 (m, 4H), 2.16 (m, 2H), 1.87 (m, 4H), 1.69 (m, 3H), 1.43-1.25 (m, 9H); FDMS 611 (M^+); Anal. Calcd for $C_{37}H_{45}N_3O_3S$: C, 72.63; H, 7.41, N, 6.87. Found: C, 72.34, H, 7.64, N, 6.61.

Part B. (±)-6-Hydroxy-3-[6-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]pyrid-3-yl]methyl-2-[4-[2-(1-pyrro-lidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

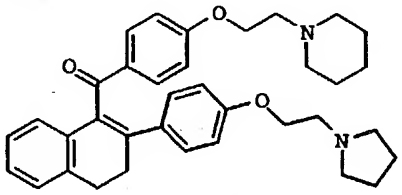
The title compound was prepared from (±)-6-hydroxy-3-[6-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]pyrid-3-yl]methyl-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene (Part A) by essentially following the procedures detailed in Example 20, Part C.

mp 128-133 °C (dec); ^{1}H NMR (DMSO-d_6) δ 7.93 (s, 1H), 7.47 (dd, J = 8.7 Hz, 2.7 Hz, 2H), 7.38 (m, 2H), 7.27 (d, J = 2.0 Hz, 1H), 7.10 (d, J = 8.6 Hz, 2H) 6.83 (d, J = 8.6 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 5.13 (m, 1H), 4.35 (br t, 2H), 4.14 (s, 2H), 3.56 (br t, 2H), 3.33-3.00 (m, 9H), 2.12 (m, 2H),

1.99-1.94 (m, 4H), 1.75-1.62 (m, 6H), 1.28-1.17 (m, 6H); FDMS 612 (M^+); Anal. Calcd for $C_{37}H_{45}N_3O_3S \cdot 2.36C_2H_2O_4$: C, 60.79; H, 6.08; N, 5.10. Found: C, 60.76; H, 6.25; N, 5.26.

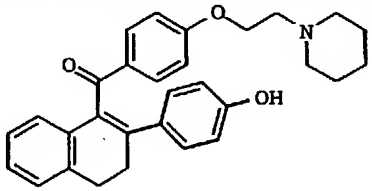
Example 24

Preparation of 2-[4-[2-(1-Pyrrodinyl)ethoxy]phenyl]-3,4-dihydronaphth-1-yl 4-[2-(1-Piperidyl)ethoxy]phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

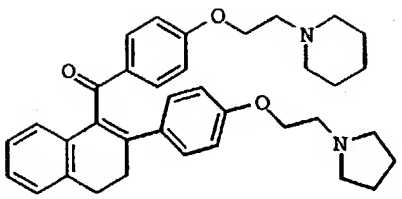
Part A. 2-(4-Hydroxyphenyl)-3,4-dihydronaphth-1-yl 4-[2-(1-Piperidyl)ethoxy]phenyl Ketone.



The title compound was prepared in 95% yield from 2-(4-methoxyphenyl)-3,4-dihydronaphth-1-yl 4-[2-(1-piperidyl)-ethoxy]phenyl ketone by essentially following the procedure detailed in Example 21, Part B.

mp 83-85 °C; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8.7 Hz, 2H), 7.21 (d, J = 7.1 Hz, 1H), 7.16-7.05 (m, 4H), 6.94 (d, J = 7.8 Hz, 1H), 6.60 (d, J = 8.8 Hz, 2H), 6.54 (d, J = 8.5 Hz, 2H), 4.01 (t, J = 5.6 Hz, 2H), 3.03 (distorted t, 2H), 2.81 (t, J = 8.4 Hz, 2H), 2.74 (t, J = 5.6 Hz, 2H), 2.53 (br s, 4H), 1.61 (m, 4H), 1.43 (m, 2H); FDMS 453 (M^+); Anal. Calcd for $C_{30}H_{31}NO_3 \cdot 0.56CH_2Cl_2$: C, 73.24; H, 6.46; N, 2.79. Found: C, 73.27; H, 6.50; N, 2.72.

Part B. 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-3,4-dihydronaphth-1-yl 4-[2-(1-Piperidyl)ethoxy]phenyl Ketone Dioxalate.



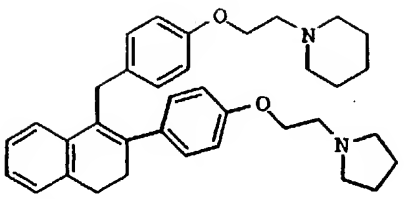
$2\ C_2H_2O_4$

To a solution of 731.0 mg (1.61 mmol) 2-(4-hydroxyphenyl)-3,4-dihydronaphth-1-yl 4-[2-(1-piperidyl)ethoxy]-phenyl ketone (Part A) in 16.0 mL of anhydrous DMF at room temperature was added Cs_2CO_3 (1.575 g, 4.83 mmol), followed by addition of 1-(2-chloroethyl)pyrrolidine hydrochloride (411 mg, 2.42 mmol). The light yellow slurry was then heated to 85 °C and stirred for 3.5 h. The reaction mixture was cooled to room temperature and 80 mL of H_2O was added. This mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with 100 mL of brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 60:37:3 THF-hexanes-TEA) to afford 821.5 mg (1.49 mmol, 93%) of a yellow gel. The free diamine was then used to prepare the title compound by essentially following the procedure detailed in Example 21, Part C.

mp 93-97 °C; ^{1}H NMR (DMSO-d_6) δ 7.77 (d, J = 8.7 Hz, 2H), 7.26-7.01 (m, 5H), 6.92 (d, J = 8.8 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 6.68 (d, J = 7.7 Hz, 1H), 4.33 (br t, 2H), 4.18 (br t, 2H), 3.45 (m, 2H), 3.36 (m, 2H), 3.25 (m, 4H), 3.13 (m, 4H), 2.99 (br t, 2H), 2.72 (br s, 2H), 1.87 (m, 4H), 1.68 (m, 4H), 1.46 (m, 2H); FDMS 551 (M^+), 641 (M + 1.0 $C_2H_2O_4$); Anal. Calcd for $C_{36}H_{42}N_2O_3 \cdot 2.68C_2H_2O_4$: C, 62.72; H, 6.03; N, 3.54. Found: C, 62.32; H, 5.71; N, 3.64.

Example 25

Preparation of 1-[4-[2-(1-Piperidyl)ethoxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-3,4-dihydronaphthalene Dioxalate.



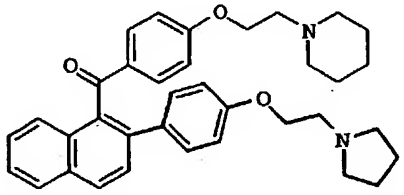
2 $C_2H_2O_4$

The title compound was prepared in 68% yield from 2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-3,4-dihydronaphth-1-yl 4-[2-(1-piperidyl)ethoxy]phenyl ketone by essentially following the procedures detailed in Example 21, Parts A and C.

mp 140-143 °C; ^{1}H NMR (DMSO-d_6) δ 7.36 (d, J = 7.9 Hz, 1H), 7.19-7.02 (m, 6H), 6.94-6.79 (m, 5H), 4.96 (s, 2H), 4.24 (m, 4H), 3.36-3.30 (m, 7H), 3.15 (m, 4H), 3.05-2.90 (m, 3H), 2.80-2.55 (m, 2H), 1.92 (m, 4H), 1.72 (m, 4H), 1.50 (m, 2H); FDMS 534 (M-2); Anal. Calcd for $C_{36}H_{44}N_2O_2 \cdot 2.0C_2H_2O_4$: C, 67.02; H, 6.75; N, 3.91. Found: C, 67.32; H, 6.69; N, 4.10.

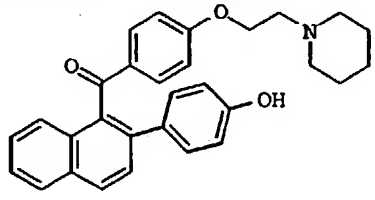
Example 26

Preparation of 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-naphth-1-yl 4-[2-(1-Piperidyl)ethoxy]phenyl Ketone Dioxalate.



2 $C_2H_2O_4$

Part A. 2-(4-Hydroxyphenyl)naphth-1-yl 4-[2-(1-Piperidyl)ethoxy]phenyl Ketone.



The title compound was prepared in 92% yield from 2-(4-methoxyphenyl)naphth-1-yl 4-[2-(1-piperidyl)ethoxy]phenyl ketone by essentially following the procedure described in Example 21, Part B.

mp 167-170 °C; ^{1}H NMR ($CDCl_3$) δ 7.98 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.61-7.41 (m, 5H), 7.17 (d, J = 8.5 Hz, 2H), 6.69-6.59 (m, 4H), 4.05 (t, J = 5.6 Hz, 2H), 2.79 (t, J = 5.4 Hz, 2H), 2.58 (br s, 4H), 1.65 (m, 4H), 1.47 (m, 2H); FDMS 451 (M^+).

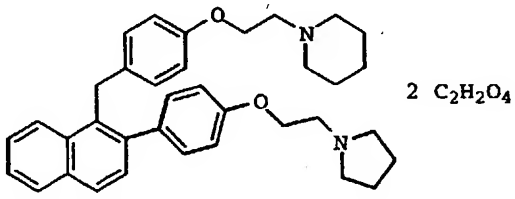
Part B. 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]naphth-1-yl 4-[2-(1-Piperidyl)ethoxy]phenyl Ketone Dioxalate.

The title compound was prepared from 2-(4-hydroxyphenyl)naphth-1-yl 4-[2-(1-piperidyl)ethoxy]phenyl ketone in 94% yield by essentially following the procedure detailed in Example 3, Part D and Example 21, Part C.

mp 95-100 °C; ^{1}H NMR (DMSO-d_6) δ 8.11 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.58-7.40 (m, 6H), 7.29 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.6 Hz, 4H), 4.30 (br t, 2H), 4.21 (br t, 2H), 3.47 (br t, 2H), 3.34 (br t, 2H), 3.27 (br s, 4H), 3.18-3.04 (m, 4H), 1.88 (br s, 4H), 1.67 (m, 4H), 1.46 (m, 2H); FDMS 549 (M^+); Anal. Calcd for $C_{36}H_{40}N_2O_3 \cdot 2.27C_2H_2O_4$: C, 64.66; H, 5.96; N, 3.72. Found: C, 64.22 H, 5.89; N, 3.56.

Example 27

Preparation of 1-[4-[2-(1-Piperidyl)ethoxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]naphthalene Dioxalate.

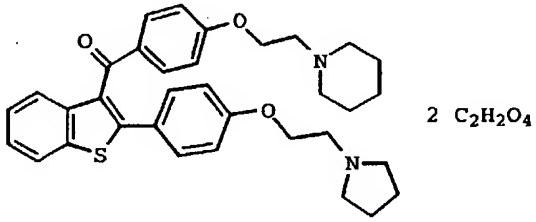


The title compound was prepared in 71% yield from 2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]naphth-1-yl 4-[2-(1-piperidyl)ethoxy]phenyl ketone by essentially following the procedures detailed in Example 21, Parts A and C.

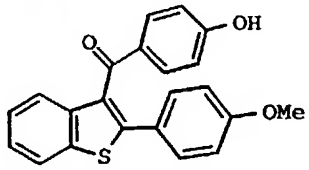
mp 184-187 °C; ^{1}H NMR (DMSO-d_6) δ 7.96 (d, J = 7.7 Hz, 1H), 7.91 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.50-7.40 (m, 3H), 7.31 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 4.36 (s, 2H), 4.32 (br t, 2H), 4.20 (br t, 2H), 3.53 (m, 2H), 3.31 (m, 6H), 3.09 (m, 4H), 1.93 (m, 4H), 1.69 (m, 4H), 1.50 (m, 2H); FDMS 535 (M^+); Anal. Calcd for $C_{36}H_{42}N_2O_2 \cdot 2.0C_2H_2O_4$: C, 67.21; H, 6.49; N, 3.92. Found: C, 66.93; H, 6.45; N, 4.05.

Example 28

Preparation of 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl 4-[2-(1-Piperidyl)ethoxy]phenyl Ketone Dioxalate.



Part A. 2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl 4-Hydroxyphenyl Ketone.

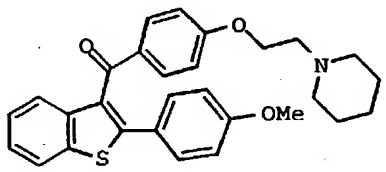


A ~0.5 M solution of sodium thioethoxide was prepared by adding ethanethiol (1.60 mL, 21.4 mmol) to a suspension of 60% NaH dispersion in mineral oil (769 mg, 19.2 mmol) in 40 mL of anhydrous DMF at 0 °C. The ice bath was removed and the solution was stirred at room temperature for 30 min. The 0.5 M solution of sodium thioethoxide was then added dropwise to the solution of 4.00 g (10.7 mmol) of 2-(4-methoxyphenyl)-benzo[*b*]thiophen-3-yl 4-methoxyphenyl ketone in 10.0 mL of anhydrous DMF at room temperature. The reaction mixture was heated at 85 °C for 3 h, then allowed to cool to room temperature, and acidified with 20 mL of 1.0 N HCl. To this

was added 200 mL of H_2O and the mixture was extracted with EtOAc (3 x 400 mL). The combined organic layers were washed with 200 mL of brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by PrepLC (30% EtOAc in hexanes) to afford 3.017 g of the title compound (8.37 mmol, 78%) as a yellow foam.

mp 76-77 °C; ^1H NMR ($CDCl_3$) δ 7.85 (m, 1H), 7.72 (d, J = 8.7 Hz, 2H), 7.64 (m, 1H), 7.38-7.29 (m, 4H), 6.76 (d, J = 8.7 Hz, 2H), 6.68 (d, J = 8.7 Hz, 2H), 6.03 (br s, 1H), 3.75 (s, 3H); FDMS 360 (M^+); Anal. Calcd for $C_{22}H_{16}O_3S$: C, 73.31; H, 6.20. Found: C, 73.57; H, 4.60.

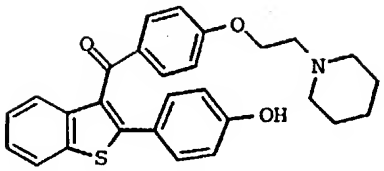
Part B. 2-(4-Methoxyphenyl)benzo[*b*]thiophen-3-yl 4-[2-(1-Piperidyl)ethoxy]phenyl Ketone.



The title compound was prepared using 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl 4-hydroxyphenyl ketone and 1-(2-chloroethyl)piperidine hydrochloride in 81% yield by essentially following the same procedures detailed in Example 24, Part B.

mp 41-44 °C; ^1H NMR ($CDCl_3$) δ 7.85 (m, 1H), 7.77 (d, J = 8.8 Hz, 2H), 7.64 (m, 1H), 7.40-7.33 (m, 4H), 6.77 (d, J = 8.6 Hz, 4H), 4.11 (t, J = 5.8 Hz, 2H), 3.76 (s, 3H), 2.77 (t, J = 5.8 Hz, 2H), 2.51 (br s, 4H), 1.61 (m, 4H), 1.44 (m, 2H); FDMS 471 (M^+); Anal. Calcd for $C_{29}H_{29}NO_3S$: C, 73.86; H, 6.20, N, 2.97. Found: C, 73.90; H, 6.20; N, 3.14.

Part C. 2-(4-Hydroxyphenyl)benzo[*b*]thiophen-3-yl 4-[2-(1-Piperidyl)ethoxy]phenyl Ketone.



The title compound was prepared from 2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl 4-[2-(1-piperidyl)ethoxy]phenyl ketone in 93% yield as a yellow foam by essentially following the same procedure detailed in Example 21, Part B.

mp 100-103 °C; ^{1}H NMR ($CDCl_3$) δ 7.84 (m, 1H), 7.70 (m, 1H), 7.68 (d, *J* = 8.9 Hz, 2H), 7.34 (m, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 6.62 (d, *J* = 8.9 Hz, 2H), 6.58 (d, *J* = 8.6 Hz, 2H), 4.07 (t, *J* = 5.6 Hz, 2H), 2.78 (t, *J* = 5.6 Hz, 2H), 2.57 (br s, 4H), 1.64 (m, 4H), 1.45 (m, 2H); FDMS 457 (M^+); Anal. Calcd for $C_{28}H_{27}NO_3S$: C, 73.49; H, 5.95; N, 3.06. Found: C, 73.76; H, 5.97; N, 3.07.

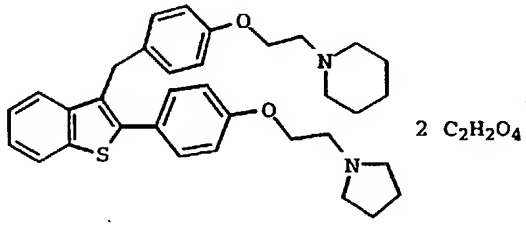
Part D. 2-[4-[2-(1-Pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl 4-[2-(1-Piperidyl)ethoxy]phenyl Ketone Dioxalate.

The title compound was prepared in quantitative yield from 2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl 4-[2-(1-piperidyl)ethoxy]phenyl ketone (Part C) by essentially following the procedure detailed in Example 4, Part B, except using 1-(2-hydroxyethyl)pyrrolidine, and Example 21, Part C.

mp 86-90 °C; ^{1}H NMR (DMSO-d_6) δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 2H), 7.43-7.35 (m, 5H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 4.34 (br t, 2H), 4.25 (br t, 2H), 3.48 (br t, 2H), 3.37 (br t, 2H), 3.27 (m, 4H), 3.13 (m, 4H), 1.89 (m, 4H), 1.68 (m, 4H), 1.47 (m, 2H); FDMS 555 (M^+); Anal. Calcd for $C_{34}H_{38}N_2O_3S \cdot 2.0C_2H_2O_4$: C, 62.11; H, 5.76; N, 3.81. Found: C, 61.81; H, 5.61; N, 3.53.

Example 29

Preparation of 3-[4-[2-(1-Piperidyl)ethoxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

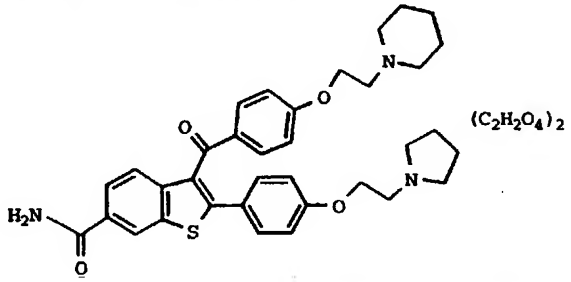


The title compound was prepared in 63% yield from 2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl)benzo[*b*]thiophen-3-yl 4-[2-(1-piperidyl)ethoxy]phenyl ketone by essentially following the procedures detailed in Example 21, Parts A and C.

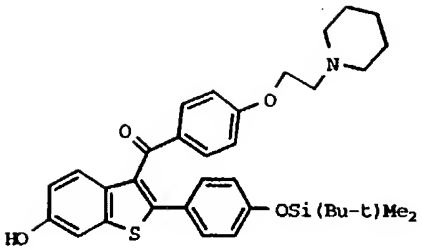
mp 188-191 °C; ^{1}H NMR (DMSO-d_6) δ 7.96 (m, 1H), 7.55 (m, 1H), 7.50 (d, *J* = 7.9 Hz, 2H), 7.34 (m, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.88 (d, 8.5 Hz, 2H), 4.34 (br t, 2H), 4.21 (m, 4H), 3.55 (m, 2H), 3.33 (m, 6H), 3.11 (m, 4H), 1.94 (m, 4H), 1.70 (m, 4H), 1.51 (m, 2H); FDMS 541 (M^+); Anal. Calcd for $C_{34}H_{40}N_2O_2S \cdot 2.0C_2H_2O_4$: C, 63.32; H, 6.15; N, 3.89. Found: C, 63.03; H, 6.05; N, 3.81.

Example 30

Preparation of 3-[4-[2-(1-Piperidinyl)ethoxy]benzoyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene-6-carboxamide Dioxalate.



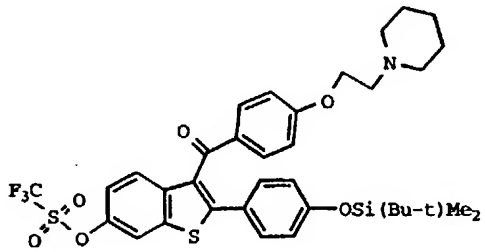
Part A. 2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]phenyl]-6-hydroxybenzo[*b*]thiophen-3-yl 4-[2-(1-Piperidinyl)ethoxy]phenyl Ketone.



To a solution of 30 g (58.8 mmol) of 6-hydroxy-2-(4-hydroxyphenyl)benzo[*b*]thiophen-3-yl 4-[2-(1-piperidinyl)-ethoxy]phenyl ketone hydrochloride in 120 mL of anhydrous THF and 60 mL of anhydrous DMF was added 20 mL (144 mmol) of anhydrous triethylamine and 9.75 g (64.7 mmol) of tert-butyldimethylsilyl chloride under a nitrogen atmosphere. The reaction mixture was heated at 60 °C in an oil bath for 4 h and then cooled to room temperature. The solution was diluted with 225 mL of toluene, filtered through a medium glass frit, and concentrated at reduced pressure. The residue was purified by PrepLC (0 to 4% MeOH in CH_2Cl_2) to give 6.77 g (11.5 mmol, 20%) of a yellow foam.

^1H NMR ($CDCl_3$) δ 7.67 (d, *J* = 8.8 Hz, 2H), 7.45 (d, *J* = 8.8 Hz, 1H), 7.23 (m, 3H), 6.83 (d, *J* = 8.8 Hz, 1H), 6.68 (m, 4H), 4.18 (br s, 2H), 2.96 (br s, 2H), 2.72 (br s, 4H), 1.75 (br s, 4H), 1.51 (br s, 2H), 0.93 (s, 9H), 0.12 (s, 6H); high resolution FDMS 588.2648 (M^+).

Part B. 2-[4-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]phenyl]-6-[[(trifluoromethyl)sulfonyl]oxy]-benzo[*b*]thiophen-3-yl 4-[2-(1-Piperidinyl)ethoxy]-phenyl Ketone.

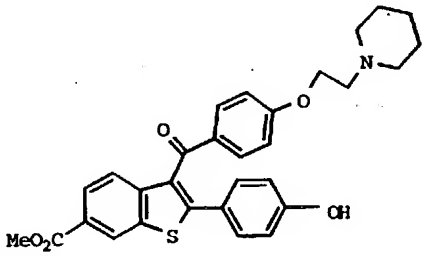


To a solution of 6.0 g (10.2 mmol) of 2-[4-[[(1,1-dimethylethyl)dimethylsilyl]oxy]phenyl]-6-hydroxybenzo-

[*b*]thiophen-3-yl 4-[2-(1-piperidinyl)ethoxy]phenyl ketone (Part A) in 60 mL of anhydrous dichloroethane was added 4.13 g (40.8 mmol) of anhydrous triethylamine and 4.01 g (11.2 mmol) of N-phenyltrifluoromethanesulfonimide under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 4 h and then filtered through a cotton plug and concentrated at reduced pressure. The residue was chromatographed over silica gel (0 to 3% MeOH in CH_2Cl_2) to give 7.20 g (10.0 mmol, 98%) of a brown foam.

^1H NMR ($CDCl_3$) δ 7.82 (d, *J* = 9.0 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.32 (m, 3H), 6.79 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.6 Hz, 2H), 4.20 (t, *J* = 5.6 Hz, 2H), 2.91 (t, *J* = 5.7 Hz, 2H), 2.66 (br s, 4H), 1.70 (m, 4H), 1.53 (m, 2H), 0.98 (s, 9H), 0.17 (s, 6H); FDMS 719.7 (M^+).

Part C. 2-(4-Hydroxyphenyl)-3-[4-[2-(1-piperidinyl)-ethoxy]benzoyl]benzo[*b*]thiophene-6-carboxylic Acid Methyl Ester.

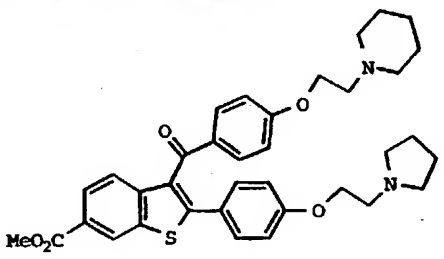


To a solution of 3.7 mL of anhydrous DMF, 1.8 mL of anhydrous triethylamine, and 1.8 mL of anhydrous methanol was added 1.0 g (1.4 mmol) of 2-[4-[[(1,1-dimethylethyl)-dimethylsilyl]oxy]phenyl]-6-[[(trifluoromethyl)sulfonyl]oxy]-benzo[*b*]thiophen-3-yl 4-[2-(1-piperidinyl)ethoxy]phenyl ketone (Part B) at room temperature. To this were added 29.4 mg (0.13 mmol) of Pd(II) acetate and 53.8 mg (0.13 mmol) of 1,3-bis(diphenylphosphino)propane, and the flask was evacuated and then filled with carbon monoxide in a balloon. The reaction mixture was heated at 55 °C for 12 h under a carbon monoxide atmosphere. After cooling the reaction mixture to room temperature, the solution was saturated with

nitrogen gas and then concentrated at reduced pressure. To this were added 5 mL of THF and 4 mL of 1N HCl, and the solution was stirred at room temperature for 3 h. The reaction mixture was treated with 10 mL of 2N ammonium hydroxide solution for an additional hour at room temperature. The solution was poured into a separatory funnel and the aqueous layer was saturated with sodium chloride and extracted three times with 50 mL portions of THF. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and concentrated at reduced pressure. The residue was purified on silica gel (0 to 10% MeOH in CH_2Cl_2) to give 578 mg (1.1 mmol, 80%) of an orange foam.

^1H NMR ($CDCl_3$) δ 8.62 (s, 1H), 8.07 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.68 (d, J = 8.6 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 6.69 (d, J = 8.6 Hz, 4H), 4.25 (t, J = 5.6 Hz, 2H), 4.01 (s, 3H), 3.07 (t, J = 4.3 Hz, 2H), 2.87 (br s, 4H), 1.82 (br s, 4H), 1.59 (br s, 2H); FDMS 516 (M^+).

Part D. 3-[4-[2-(1-Piperidinyl)ethoxy]benzoyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene-6-carboxylic Acid Methyl Ester.

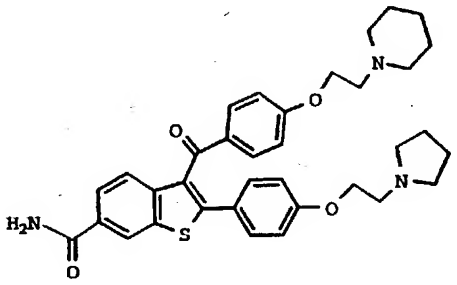


To a solution of 1.5 g (2.9 mmol) of 2-(4-hydroxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]benzoyl]-benzo[*b*]thiophene-6-carboxylic acid methyl ester (Part C) and 544 mg (3.2 mmol) of 1-(2-chloroethyl)pyrrolidine hydrochloride in 20 mL of anhydrous DMF was added 2.37 g (7.3 mmol) of cesium carbonate at room temperature under a nitrogen atmosphere. The reaction mixture was heated at

60 °C for 4 h and then cooled to room temperature and diluted with 125 mL of THF and 75 mL of water. The aqueous layer was saturated with sodium chloride and extracted twice with 50 mL portions of THF. The combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and concentrated at reduced pressure. The residue was purified on silica gel (1:1 MeOH/TEA (10%) in THF) to give 1.26 g (2.2 mmol, 77%) of an orange-brown foam.

^{1}H NMR ($CDCl_3$) δ 8.57 (s, 1H), 7.98 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.77 (d, *J* = 8.8 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 6.78 (dd, *J* = 8.7, 6.7 Hz, 4H), 4.18 (m, 4H), 4.01 (s, 3H), 2.86 (t, *J* = 6.0 Hz, 2H), 2.74 (t, *J* = 6.0 Hz, 2H), 2.59 (m, 4H), 2.47 (m, 4H), 1.79 (m, 4H), 1.58 (m, 4H), 1.48 (m, 2H); FDMS 614 (M^{+1}).

Part E. 3-[4-[2-(1-Piperidinyl)ethoxy]benzoyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene-6-carboxamide.



To a solution of 4.37 g (7.1 mmol) of 3-[4-[2-(1-piperidinyl)ethoxy]benzoyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene-6-carboxylic acid methyl ester (Part D) in 100 mL of methanol was added 35 mL of liquid anhydrous ammonia. The solution was sealed in a shaker and heated to 60 °C for 3 days. The solution was then saturated with nitrogen gas, concentrated at reduced pressure, and chromatographed on silica gel (1:1 TEA/MeOH in THF, 0 to 10%) to give 3.22 g (5.4 mmol, 76%) of a yellow-brown foam.

^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1H), 7.72 (m, 4H), 7.37 (d, *J* = 8.6 Hz, 2H), 6.78 (dd, *J* = 8.1, 2.1 Hz, 4H), 4.07 (m, 4H), 2.86 (t, *J* = 5.6 Hz, 2H), 2.74 (t, *J* = 5.8 Hz, 2H), 2.61 (br s, 4H), 2.48 (br s, 4H), 1.80 (br s, 4H), 1.59 (m, 4H), 1.43 (m, 2H); FDMS 597 (M^+).

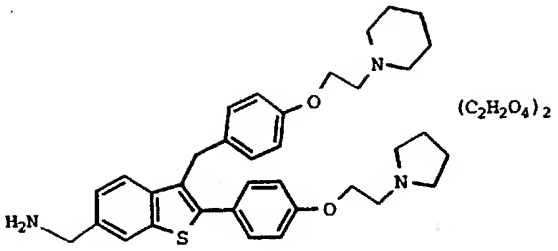
Part F. 3-[4-[2-(1-Piperidinyl)ethoxy]benzoyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene-6-carboxamide Dioxalate.

A solution of 3-[4-[2-(1-piperidinyl)ethoxy]benzoyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene-6-carboxamide (Part E) (131 mg, 0.219 mmol) in EtOAc (8 mL) was treated with a solution of oxalic acid (49.3 mg, 0.548 mmol) in EtOAc (8 mL) to form a white suspension. After filtration and drying, 135 mg (79%) of the title compound was obtained as a white solid.

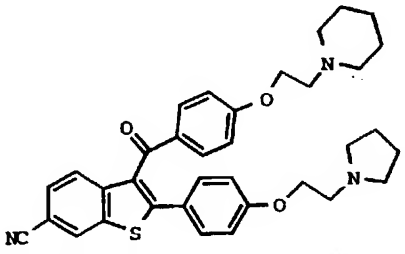
mp 87.0-93.0 °C; IR (KBr) 3420 (br), 3359 (br), 2681 (br), 1722, 1650, 1599 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 9.20 (br s, 4H), 8.56 (s, 1H), 8.06 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.35-7.45 (m, 4H), 6.96 (d, *J* = 8.3 Hz, 4H), 4.26-4.38 (m, 2H), 4.20-4.26 (m, 2H), 3.40-3.50 (m, 2H), 3.30-3.38 (m, 2H), 3.19-3.30 (m, 4H), 3.02-3.18 (m, 4H), 1.82-1.92 (m, 4H), 1.62-1.72 (m, 4H), 1.20-1.48 (m, 2H); FDMS *m/e* 598 (M^+-$C_4H_3O_8$); Anal. Calcd for $C_{39}H_{43}N_3O_{12}S$: C, 60.22; H, 5.57; N, 5.40; S, 4.12. Found: C, 60.07; H, 5.68; N, 5.18; S, 4.02.

Example 31

Preparation of 3-[[4-[2-(1-Piperidinyl)ethoxy]phenyl]-methyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenylbenzo-[*b*]thiophene-6-methanamine Dioxalate.



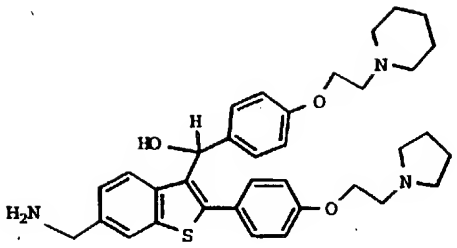
Part A. 3-[4-[2-(1-Piperidinyl)ethoxy]benzoyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene-6-carbonitrile.



To a solution of 3.1 g (5.2 mmol) of 3-[4-[2-(1-piperidinyl)ethoxy]benzoyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene-6-carboxamide (Example 30, Part E) in 75 mL of anhydrous THF was added 3.1 g (13.0 mmol) of (methoxycarbonylsulfamoyl)triethylammonium hydroxide (inner salt) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 3 days and then filtered through a medium frit, concentrated at reduced pressure, and chromatographed on silica gel (1:1 TEA/MeOH in THF, 0 to 10%) to give 2.70 g (4.7 mmol, 90%) of a brown foam.

^{1}H NMR ($CDCl_3$) δ 8.18 (s, 1H), 7.72 (d, *J* = 8.9 Hz, 3H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.6 Hz, 2H), 6.80 (t, *J* = 8.3 Hz, 4H), 4.22 (br s, 4H), 3.10 (br s, 2H), 2.89 (br s, 6H), 2.64 (br s, 4H), 1.95 (br s, 4H), 1.70 (br s, 4H), 1.43 (br s, 2H); FDMS 580 (M^+).

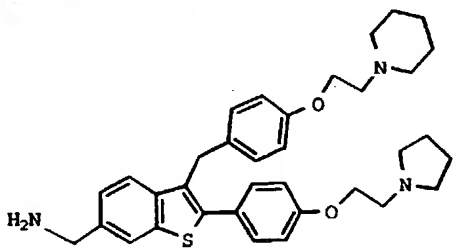
Part B. 6-(Aminomethyl)-α-[4-[2-(1-piperidinyl)-ethoxy]phenyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophene-3-methanol.



To a solution of 1.35 g (2.3 mmol) of 3-[4-[2-(1-piperidinyl)ethoxy]benzoyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene-6-carbonitrile (Part A) in 30 mL of anhydrous THF under a nitrogen atmosphere was added 414 mg (11.6 mmol) of lithium aluminum hydride. The reaction was stirred for 2.5 hours at room temperature and then quenched with 5 mL of ethyl acetate and 5 mL of saturated aqueous potassium sodium tartrate for 16 h. The reaction mixture was poured into 50 mL of water, saturated with sodium chloride, and extracted with three 50 mL portions of THF. The combined organic layers were washed with brine, dried with anhydrous magnesium sulfate, and concentrated to give 1.32 g (95% crude yield) of a brown foam.

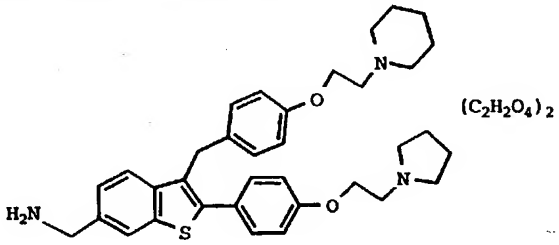
^{1}H NMR ($CDCl_3$) δ 7.68 (m, 2H), 7.38 (d, J = 8.6 Hz, 2H), 7.31 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 6.17 (s, 1H), 4.05 (m, 4H), 3.87 (s, 2H), 2.86 (t, J = 5.9 Hz, 2H), 2.72 (t, J = 6.1 Hz, 2H), 2.57 (br s, 4H), 2.47 (br s, 4H), 1.75 (br s, 4H), 1.57 (m, 4H), 1.43 (br s, 2H).

Part C. 3-[[4-[2-(1-Piperidinyl)ethoxy]phenyl]-methyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophene-6-methanamine.



To a solution of 1.32 g (2.3 mmol) of 6-(aminomethyl)-α-[4-[2-(1-piperidinyl)ethoxy]phenyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene-3-methanol in 40 mL of anhydrous dichloroethane at 0 °C was added 1.84 g (15.8 mmol) of triethylsilane and 2.62 g (23.0 mmol) of trifluoroacetic acid, respectively, under a nitrogen atmosphere. After one hour at 0 °C, the reaction was warmed to room temperature and stirred for 24 h. The reaction was quenched with 10 mL of saturated aqueous sodium bicarbonate and poured into 30 mL of water. The aqueous layer was saturated with sodium chloride, separated from the dichloroethane layer, and extracted with three 50 mL portions of THF. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated at reduced pressure to give 786 mg (60% crude yield) of a brown foam. This material was carried on to the salt in Part D.

Part D. 3-[[4-[2-(1-Piperidinyl)ethoxy]phenyl]-methyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophene-6-methanamine Dioxalate.



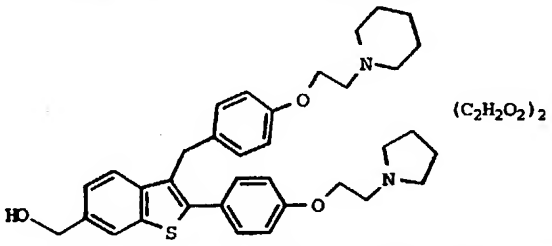
3-[[4-[2-(1-Piperidinyl)ethoxy]phenyl]methyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene-6-methanamine (Part C) was dissolved in 50 mL of ethyl acetate and added to a solution of 100 mg of oxalic acid in 30 mL of ethyl acetate. After adding 10 mL of ether to the solution, the precipitate was filtered to give 1.05 g (99%) of a white solid.

mp 140-142 °C; ^{1}H NMR (DMSO) δ 8.04 (s, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.6 Hz, 2H),

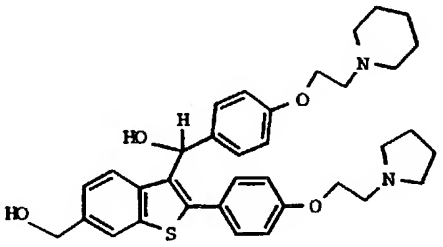
6.83 (d, J = 8.6 Hz, 2H), 4.20 (m, 4H), 4.13 (s, 2H), 4.06 (t, J = 5.6 Hz, 2H), 3.17 (t, J = 5.3 Hz, 2H), 2.92 (br s, 4H), 2.86 (t, J = 5.6 Hz, 2H), 2.64 (br s, 4H), 1.81 (br s, 4H), 1.55 (m, 4H), 1.41 (d, J = 5.1 Hz, 2H); FDMS 570.4 (M^+).

Example 32

Preparation of 3-[[4-[2-(1-Piperidinyl)ethoxy]phenyl]-methyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophene-6-methanol Dioxalate.



Part A. α(3)-[4-[2-(1-Piperidinyl)ethoxy]phenyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene-3,6-dimethanol.

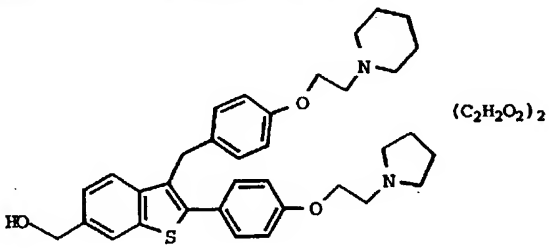


Diisobutylaluminum hydride (1.0 M in toluene, 3.59 mL) was added dropwise to a stirred solution of 3-[4-[2-(1-piperidinyl)ethoxy]benzoyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene-6-carboxylic acid methyl ester (550 mg, 0.898 mmol) in anhydrous THF (6 mL) at 0 °C under argon. The mixture was stirred at 0 °C for 1.5 h. Methanol (2 mL) and saturated aqueous potassium sodium tartrate solution (15 mL) were sequentially added to the mixture, and the resultant two-layered solution was stirred vigorously at ambient temperature for 2 h. The mixture was extracted with a mixed solvent of ethyl acetate/THF (1:1, 30 mL x 2). The combined organic layers were dried over $MgSO_4$, filtered, and

concentrated to give 496 mg (crude yield 94%) of the diol as a gum.

^1H NMR ($CDCl_3$) δ 7.79 (s, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.4 Hz, 1H), 7.13-7.19 (m, 2H), 6.84 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 6.17 (s, 1H), 4.72 (s, 2H), 3.98-4.08 (m, 4H), 3.25 (br s, 1H), 2.90 (t, J = 5.8 Hz, 2H), 2.76 (t, J = 5.8 Hz, 2H), 2.60-2.68 (m, 4H), 2.45-2.55 (m, 4H), 1.78-1.85 (m, 4H), 1.55-1.65 (m, 4H), 1.38-1.46 (m, 2H).

Part B. 3-[[4-[2-(1-Piperidinyl)ethoxy]phenyl]-methyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo-[*b*]thiophene-6-methanol Dioxalate.



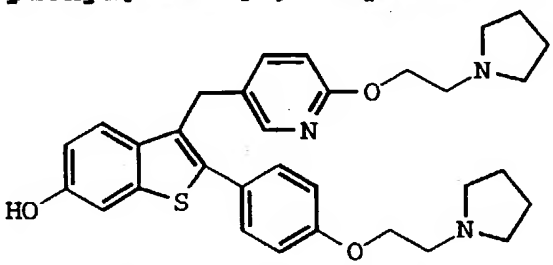
Triethylsilane (0.946 mL, 5.92 mmol) and trifluoroacetic acid (0.652 mL, 8.46 mmol) were added consecutively to a stirred solution of α(3)-[4-[2-(1-piperidinyl)ethoxy]-phenyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]-thiophene-3,6-dimethanol (Part A) (496 mg, 0.846 mmol) in dry 1,2-dichloroethane (5 mL) at 0 °C under argon atmosphere, and the resultant solution was stirred at 0 °C for 6 h. After dilution with THF (25 mL), the mixture was washed with saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer was extracted with THF (15 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. The gummy residue was chromatographed on silica [gradient TEA/i-PrOH (1:2) 0-4% in THF] to isolate 110 mg (23%) of the free base as a gum. The free base was then dissolved in EtOAc (5 mL) and treated with a solution of oxalic acid (39.9 mg, 0.443 mmol) in EtOAc (5 mL) to form a

white suspension. After filtration and drying, 120 mg (83%) of the title compound was obtained as a white solid.

mp 102.0-106.0 °C; IR (KBr) 3410 (br), 2700 (br), 1725 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40-1.50 (m, 2H), 1.60-1.70 (m, 4H), 1.85-1.95 (m, 4H), 3.00-3.18 (m, 4H), 3.22-3.40 (m, 6H), 3.45-3.53 (m, 2H), 4.15 (s, 2H), 4.18-4.25 (m, 2H), 4.25-4.35 (m, 2H), 4.55 (s, 2H), 6.82 (d, J = 8.3 Hz, 2H), 6.98 (d, J = 8.3 Hz, 2H), 7.07 (d, J = 8.5 Hz, 2H), 7.23 (d, J = 8.2 Hz, 1H), 7.43 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.2 Hz, 1H),7.84 (s, 1H), 8.60 (br s, 4H); FDMS *m/e* 571 (M^+-$C_4H_3O_8$); Anal. Calcd for $C_{39}H_{46}N_2O_{11}S$: C, 62.38; H, 6.17; N, 3.73; S, 4.27. Found: C, 62.63; H, 6.36; N, 3.91; S, 4.07.

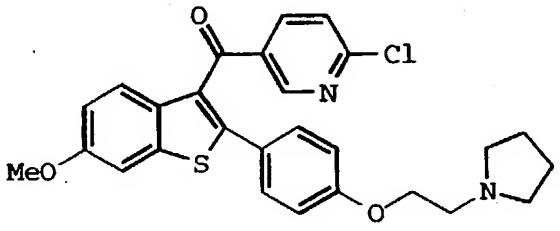
Example 33

Preparation of 6-Hydroxy-3-[6-[2-(1-pyrrolidinyl)-ethoxy]pyrid-3-ylmethyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



2 $C_2H_2O_4$

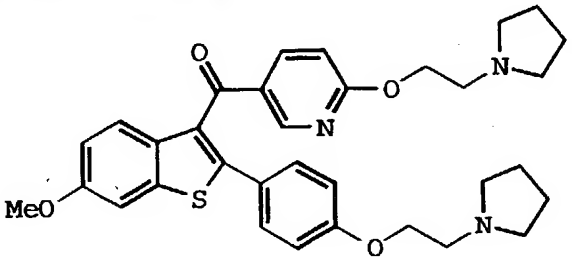
Part A. 6-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 6-Chloropyrid-3-yl Ketone.



The title compound was prepared from 6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene (Example 1, Part B) and 6-chloronicotinic acid in 51% yield (based on 6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-

benzo[*b*]thiophene) by essentially following the proceedures described in Example 1, Part C.

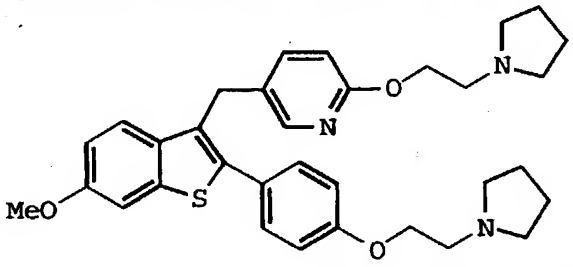
Part B. 6-Methoxy-2-[4-[2-(1pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 6-[2-(1-Pyrrolidinyl)-ethoxy]pyrid-3-yl Ketone.



The title compound was prepared in 84% yield from 6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]-thiophen-3-yl 6-chloropyrid-3-yl ketone (Part A) and 1-(2-hydroxyethyl)pyrrolidine by essentially following the procedures described in Example 9, Part B.

FDMS 572 (M+1; 100); Anal. Calcd for $C_{33}H_{37}N_3O_4S$: C, 69.33; H, 6.52; N, 7.35. Found: C, 69.10; H, 6.76; N, 7.08.

Part C. 6-Methoxy-3-[6-[2-(1-pyrrolidinyl)ethoxy]-pyrid-3-ylmethyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene Dioxalate Hemihydrate.



2 $C_2H_2O_4$

The title was prepared in 37% yield from 6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl 6-[2-(1-pyrrolidinyl)ethoxy]pyrid-3-yl ketone (Part B) by essentially following the procedure described in Example 3, Part E.

FDMS 558 (M+1; 100); Anal. Calcd for $C_{33}H_{39}N_3O_3S \cdot 2C_2H_2O_4 \cdot 0.5 H_2O$: C, 59.51; H, 5.94; N, 5.63. Found: C, 59.39; H, 5.76; N, 5.76.

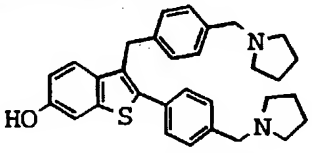
Part D. 6-Hydroxy-3-[6-[2-(1-pyrrolidinyl)-ethoxy]pyrid-3-ylmethyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

The title compound was prepared in 59% yield from 6-methoxy-3-[6-[2-(1-pyrrolidinyl)ethoxy]pyrid-3-ylmethyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene (Part C) by essentially following the procedure described in Example 1, Part D.

^1H NMR (DMSO-d_6) δ 7.88 (d, J = 1.8 Hz, 1H), 7.43-7.32 (m, 4H), 7.23 (d, J = 2.1 Hz, 1H), 7.07 (d, J = 8.4 Hz, 2H), 6.78 (dd, J = 8.4 and 2.1 Hz, 1H), 6.71 (d, J = 8.6 Hz, 1H), 4.42 (t, J = 4.9 Hz, 2H), 4.30 (t, J = 4.6 Hz, 2H), 4.09 (s, 2H), 3.53 (t, J = 4.3 Hz, 2H), 3.46 (t, J = 4.6 Hz, 2H), 2.50-2.33 (m, 8H), 1.96-1.73 (m, 8H); FDMS: 544 (M + 1; 100).

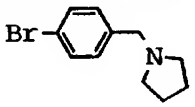
Example 34

Preparation of 6-Hydroxy-3-[4-[(1-pyrrolidinyl)-methyl]benzyl]-2-[4-[(1-pyrrolidinyl)methyl]phenyl]-benzo[*b*]thiophene Dioxalate.



$2(C_2H_2O_4)$

Part A. 1-Bromo-4-[(1-pyrrolidinyl)methyl]benzene.

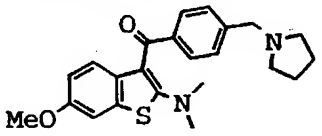


Pyrrolidine (20.0 mL, 0.240 mole) was added to a stirred solution of 4-bromobenzyl bromide (10.0 g, 40.0 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C under nitrogen. The resultant solution was allowed to stir at room temperature

for 1 h. The reaction mixture was diluted with EtOAc (150 mL) before it was washed with half-saturated aqueous $NaHCO_3$ (50 mL). After drying over $MgSO_4$, filtration, and concentration, the oily residue was chromatographed on silica [20% EtOAc in hexanes, then 10% EtOH/Et_3N (2/1) in THF/hexanes (1/1)] to provide 9.02 g of the benzyl pyrrolidine (94%) as an oil.

IR (neat) 2966,1488 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79 (br s, 4H), 2.49 (br s, 4H), 3.57 (s, 2H), 7.21 (d, J = 8.2 Hz, 2H), 7.43 (d, J = 8.2 Hz, 2H);

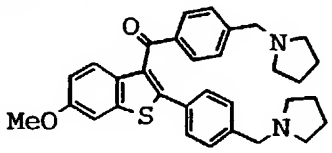
Part B. 2-Dimethylamino-6-methoxybenzo[*b*]thiophen-3-yl 4-[(1-Pyrrolidinyl)methyl]phenyl Ketone.



4-(Chloromethyl)benzoyl chloride (105 mg, 0.558 mmol) was added to a stirred solution of 2-dimethylamino-6-methoxybenzo[*b*]thiophene (105 mg, 0.507 mmol) in chlorobenzene (1 mL) under nitrogen. The resultant mixture was heated in an oil bath at 110 °C for 2.5 h. The mixture was cooled to 0 °C, treated with pyrrolidine (5 mL), then allowed to stir at room temperature for 2 h. After dilution with THF (20 mL), the mixture was washed with saturated aqueous $NaHCO_3$ (5 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated, and chromatographed on silica [gradient 20-40% EtOAc in hexanes, then 0-10% EtOH/Et_3N (2/1) in THF/hexanes (1/1)] to give 148 mg (74%) of the ketone as a foam.

IR (neat) 2957, 1625, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.83 (br s, 4H), 2.53 (br s, 4H), 2.87 (s, 6H), 3.69 (s, 2H), 3.83 (s, 3H), 6.81 (dd, J = 9.0 and 3.0 Hz, 1H), 7.12 (d, J = 3.0 Hz, 1H), 7.36 (d, J = 9.0 Hz, 1 H), 7.41 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 8.1 Hz, 2H); FDMS *m/e* 394 (M^+).

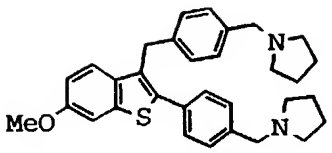
Part C. 6-Methoxy-2-[4-[(1-pyrrolidinyl)methyl]-phenyl]benzo[*b*]thiophen-3-yl 4-[(1-Pyrrolidinyl)-methyl]phenyl Ketone.



The aryl bromide of Part A (146 mg, 0.608 mmol) was added to a stirred suspension of magnesium ribbons (13.9 mg, 0.570 mmol) in anhydrous THF (2 mL) under argon atmosphere, followed by the addition of a small iodine crytal. The resultant mixture was heated in an oil bath at 60-65 °C for 2 h to form a homogeneous Grignard solution. The Grignard solution was cooled to room temperature before it was added to a stirred solution of the benzothiophene of Part B (150 mg, 0.380 mmol) in anhydrous THF (2 mL) at 0 °C under argon atmosphere. The resultant mixture was stirred at 0 °C for 1.5 h, then quenched with saturated aqueous NH_4Cl (3 mL). After extraction with EtOAc (15 mL x 2), the combined organic layers were dried over $MgSO_4$, filtered, concentrated, and chromatographed on silica [gradient 0-4% EtOH/Et_3N (2/1) in THF/hexanes (1/1)] to give 170 mg (88%) of the trisubstituted benzothiophene as a foam.

IR (neat) 2964, 1647, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77 (br s, 8H), 2.40-2.50 (m, 8H), 3.52 (s, 2H), 3.55 (s, 2H), 3.91 (s, 3H), 7.05 (dd, J = 8.9 and 2.3 Hz, 1H), 7.17 (d, J = 8.1 Hz, 2H), 7.22 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.34 (d, J = 2.3 Hz, 1H), 7.65 (d, J = 8.9 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H); FDMS *m/e* 510 (M^+).

Part D. 6-Methoxy-3-[4-[(1-pyrrolidinyl)methyl]-benzyl]-2-[4-[(1-pyrrolidinyl)methyl]phenyl]benzo-[*b*]thiophene.



DIBAL-H (0.911 mL, 1 M in toluene) was added to a stirred solution of the ketone of Part C (310 mg, 0.607 mmol) in anhydrous CH_2Cl_2 (4 mL) at 0 °C under nitrogen atmosphere, and the resultant solution was stirred at 0 °C for 40 min. The reaction mixture was treated sequentially with MeOH (0.5 mL) and saturated aqueous Rochelle's salt solution (10 mL), and then the two-layered solution was stirred vigorously at room temperature for 1 h. After extraction with EtOAc (50 mL), the organic layer was dried over $MgSO_4$, filtered, and concentrated to yield 280 mg of the corresponding alcohol.

The above alcohol was dissolved in anhydrous CH_2Cl_2 (3 mL) and cooled down to 0 °C before it was sequentially treated with Et_3SiH (0.611 mL, 3.83 mmol) and TFA (0.421 mL, 5.46 mmol). The resultant mixture was stirred at 0 °C for 1 h. After cautious treatment with saturated aqueous $NaHCO_3$ (8 mL), the mixture was allowed to warm to room temperature and extracted with EtOAc (15 mL x 2). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and chromatographed on silica [gradient 0-4% EtOH/Et_3N (2/1) in THF/hexanes (1/1)] to give 220 mg (81%) of the corresponding methylene compound as a foam.

IR (neat) 2963, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75-1.87 (m, 8H), 2.45-2.60 (m, 8H), 3.57 (s, 2H), 3.64 (s, 2H), 3.87 (s, 3H), 4.24 (s, 2H), 6.90 (dd, *J* = 8.9 and 2.4 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 2.4 Hz, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.39 (d, *J* = 8.9 Hz, 1H), 7.45 (d, *J* = 8.2 Hz, 2H); FDMS *m/e* 496 (M^+).

Part E. 6-Hydroxy-3-[4-[(1-pyrrolidinyl)methyl]-benzyl]-2-[4-[(1-pyrrolidinyl)methyl]phenyl]benzo-[*b*]thiophene Dioxalate.

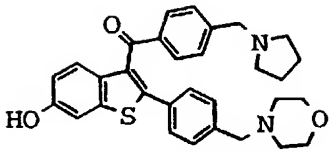
$AlCl_3$ (354 mg, 2.66 mmol) was added to a stirred solution of the methoxy benzothiophene (220 mg, 0.443 mmol) in anhydrous CH_2Cl_2 (5 mL) at room temperature under nitrogen atmosphere. The resultant suspension was stirred for 3-5 min before it was treated with EtSH (0.295 mL, 3.99 mmol), and the mixture was stirred for an additional 35 min. After dilution with THF (15 mL), the mixture was cooled to 0 °C and sequentially treated with saturated aqueous $NaHCO_3$ (15 mL) and saturated aqueous Rochelle's salt solution (10 mL). The two-layered solution was stirred vigorously for 70 min. The organic layer was separated and the aqueous layer was extracted with THF (25 mL x 2). The combined organic layers were dried over $MgSO_4$, filtered, concentrated, and chromatographed on silica [gradient 0-4% EtOH/Et_3N (2/1) in THF/hexanes (1/1)] to give 205 mg (96%) of the hydroxy benzothiophene as a foam.

A solution of oxalic acid (76.5 mg, 0.850 mmol) in EtOAc (4 mL) was added dropwise to a stirred solution of the above hydroxy benzothiophene in EtOAc (4 mL). The resultant white suspension was filtered and the white solid was dried at 80 °C under vacuum to provide 240 mg (85%) of the dioxalate.

IR (neat) 3400-2500 (br), 1721, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75-1.95 (m, 8H), 2.95-3.20 (m, 8H), 4.17 (s, 2H), 4.21 (s, 2H), 4.26 (s, 2H), 6.81 (dd, J = 8.7 and 2.1 Hz, 1H), 7.11 (d, J = 7.9 Hz, 2H), 7.28 (d, J = 2.1 Hz, 1H), 7.35 (d, J = 7.9 Hz, 2H), 7.37 (d, J = 8.7 Hz, 1H), 7.50 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.1 Hz, 2H); FDMS *m/e* 483 ($M+1-2C_2H_2O_4$); Anal. Calcd for $C_{31}H_{34}N_2OS \cdot 1.8C_2H_2O_4$: C, 64.46; H, 5.88; N, 4.34. Found: C, 64.17; H, 5.92; N, 4.47.

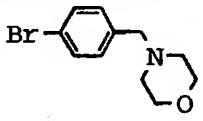
Example 35

Preparation of 6-Hydroxy-2-[4-[(4-morpholinyl)methyl]-phenyl]benzo[*b*]thiophen-3-yl 4-[(1-Pyrrolidinyl)-methyl]phenyl Ketone Dioxalate.



$2(C_2H_2O_4)$

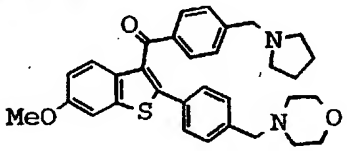
Part A. 4-[(4-Bromophenyl)methyl]morpholine.



Following the procedure of Example 34, Part A, the benzyl morpholine was obtained as an oil in 100% yield.

IR (KBr) 2803, 1487, 1111 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43 (t, J = 4.5 Hz, 4H), 3.45 (s, 2H), 3.71 (t, J = 4.5 Hz, 4H), 7.22 (d, J = 8.1 Hz, 2H), 7.45 (d, J = 8.1 Hz, 2H); FDMS *m/e* 255 (M^+, ^{79}Br) and 257 (M^+, ^{81}Br); Anal. Calcd for $C_{11}H_{14}BrNO$: C, 51.58; H, 5.51; N, 5.47. Found: C, 51.77; H, 5.66; N, 5.68.

Part B. 6-Methoxy-2-[4-[(4-morpholinyl)methyl]-phenyl]benzo[*b*]thiophen-3-yl 4-[(1-Pyrrolidinyl)-methyl]phenyl Ketone.



Following the procedure of Example 34, Part C, the trisubstituted benzothiophene was obtained from the above aryl bromide as a foam in 88% yield.

IR (neat) 2954, 1649, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77(br s, 4H), 2.35 (br s, 4H), 2.40 (br s, 4H), 3.39 (s, 2H), 3.56 (s, 2H), 3.68 (t, J = 4.2 Hz, 4H) 3.92 (s, 3H), 7.02 (dd, J = 8.7 and 2.1 Hz, 1H), 7.14-7.37 (m, 7H), 7.64 (d, 8.7 Hz, 1H), 7.70 (d, 7.8 Hz, 2H); FDMS *m/e* 527 (M+1).

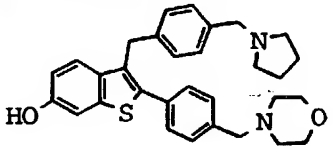
Part C. 6-Hydroxy-2-[4-[(4-morpholinyl)methyl]-phenyl]benzo[*b*]thiophen-3-yl 4-[(1-Pyrrolidinyl)-methyl]phenyl Ketone Dioxalate.

Following the procedure of Example 34, Part E, the hydroxy ketone was obtained as a yellowish solid in 55% yield.

IR (KBr) 3420 (br), 2990 (br), 2830-2200 (br), 1641, 1608 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.79 (br s, 4H), 2.37 (br s, 4H), 2.53 (br s, 4H), 3.39 (s, 2H), 3.60 (s, 2H), 3.68 (t, J = 4.2 Hz, 4H), 6.40 (dd, J = 8.7 and 2.1 Hz, 1H), 6.69 (d, J = 2.1 Hz, 1H), 7.12 (d, J = 8.1 Hz, 2H) 7.21-7.25 (m, 4H), 7.43 (d, J = 8.7 Hz, 1H), 7.67 (d, J = 7.8 Hz, 2H); FDMS *m/e* 513 (M+1-$2C_2H_2O_4$).

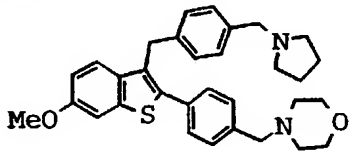
Example 36

Preparation of 6-Hydroxy-2-[4-[(4-morpholinyl)methyl]-phenyl]-3-[4-[(1-pyrrolidinyl)methyl]benzyl]-benzo[*b*]thiophene Dioxalate.



$2(C_2H_2O_4)$

Part A. 6-Methoxy-2-[4-[(4-morpholinyl)methyl]-phenyl]-3-[4-[(1-pyrrolidinyl)methyl]benzyl]-benzo[*b*]thiophene.



Following the procedure of Example 34, Part D, the methoxy benzothiophene was obtained from the above ketone as a foam in 57% yield.

IR (neat) 2958, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.76-1.80 (m, 4H), 2.37-2.50 (m, 8H), 3.53 (s, 2H), 3.57 (s, 2H), 3.73 (t,

J = 4.8 Hz, 4H) 3.87 (s, 3H), 4.25 (s, 2H), 6.90 (dd, J = 8.7 and 2.4 Hz, 1H), 7.10 (d, J = 8.1 Hz, 2H), 7.18-7.41 (m, 6H), 7.45 (d, J = 8.1 Hz, 2H); FDMS *m/e* 513 (M+1).

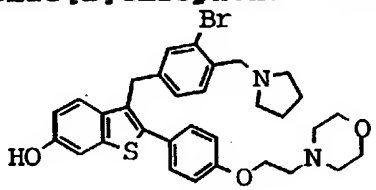
Part B. 6-Hydroxy-2-[4-[(4-morpholinyl)methyl]-phenyl]-3-[4-[(1-pyrrolidinyl)methyl]benzyl]-benzo[*b*]thiophene Dioxalate.

Following the procedure of Example 34, Part E, the hydroxy benzothiophene salt was obtained as a white solid in 57% yield.

IR (KBr) 3445 (br), 2950, 2840-2220 (br), 1720, 1630, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.88 (br s, 4H), 2.56 (br s, 4H), 3.13 (br s, 4H), 3.61 (br s, 4H), 3.70 (s, 2H), 4.22 (br s, 4H), 6.79 (dd, J = 8.4 and 2.0 Hz, 1H), 7.13 (d, J = 7.5 Hz, 2H), 7.27 (d, J = 2.0 Hz, 1H), 7.34-7.44 (m, 7H); FDMS *m/e* 499 (M+1-$2C_2H_2O_4$); Anal. Calcd for $C_{31}H_{34}N_2O_2S \cdot 2C_2H_2O_4$: C, 61.93; H, 5.64; N, 4.13. Found: C, 62.09; H, 5.77; N, 3.96.

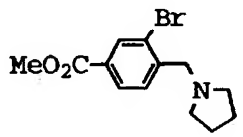
Example 37

Preparation of 3-[3-Bromo-4-[(1-pyrrolidinyl)-methyl]benzyl]-6-hydroxy-2-[4-[2-(4-morpholinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



$2(C_2H_2O_4)$

Part A. Methyl 3-Bromo-4-[(1-pyrrolidinyl)methyl]-benzoate.



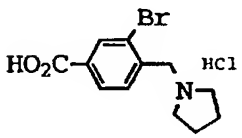
AIBN (79 mg) was added to a stirred suspension of methyl 3-bromo-4-methylbenzoate (11.0 g, 48.0 mmol) and NBS (10.3 g, 57.6 mmol) in CCl_4 (400 mL), and the resultant mixture was

heated to reflux for 2 h. After cooling to room temperature, the mixture was diluted with hexanes (200 mL) before it was filtered and concentrated to give 14.7 g (crude yield 100%) of methyl 3-bromo-4-(bromomethyl)benzoate.

Part of the crude dibromide (14.7 g) was dissolved in anhydrous CH_2Cl_2 (60 mL). The solution was cooled to 0 °C and treated with pyrrolidine (9.96 mL, 119 mmol), then it was allowed to stir at room temperature for 2 h. The reaction mixture was diluted with EtOAc (500 mL), washed with half-saturated aqueous $NaHCO_3$ (100 mL), dried over $MgSO_4$, filtered, and concentrated to give an oily residue. The crude product was chromatographed on silica [gradient 0-10% EtOH/Et_3N (2/1) in THF/hexanes (1/1)] to provide 6.45 g of the pyrrolidinyl ester (45%) as an oil.

IR (neat) 2953, 1728, 1602 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.82 (br s, 4H), 2.61 (br s, 4H), 3.77 (s, 2H), 3.92 (s, 3H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.95 (dd, *J* = 8.0 and 1.4 Hz, 1H), 8.20 (d, *J* = 1.4 Hz, 1H); FDMS *m/e* 297 (M^+, ^{79}Br) and 299(M^+, ^{81}Br).

Part B. 3-Bromo-4-[(1-pyrrolidinyl)methyl]benzoic Acid Hydrochloride.

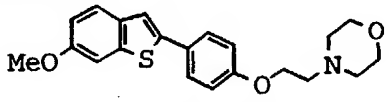


LiOH (32.4 mL, 1 N) was added to a stirred solution of the above ester (6.45 g, 21.6 mmol) in THF (75 mL) / MeOH (25 mL), and the resultant solution was heated in an oil bath at 50 °C for 3 h. After cooling to room temperature, the solution was treated in portions with 5 N HCl (22 mL), and then concentrated at 50 °C under vacuum to give 8.20 g (crude yield 99%) of the benzoic acid as a white solid contaminated with LiCl.

IR (KBr) 3397 (br), 2924, 2679-2000 (br), 1713, 1634, 1464 cm^{-1}; ^1H NMR (DMSO-d_6) δ1.94 (br s, 4H), 2.95-3.70 (m, 4H),

4.54 (s, 2H), 7.92 (d, J = 8.1 Hz, 1H), 8.10 (s, 1H), 8.12 (d, J = 8.1 Hz, 1H).

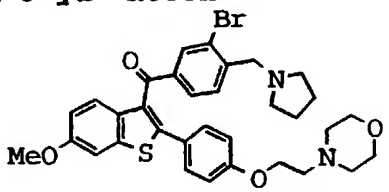
Part C. 6-Methoxy-2-[4-[2-(4-morpholinyl)ethoxy]-phenyl]benzo[*b*]thiophene.



Cs_2CO_3 (4.89 g, 15.0 mmol) was added to a stirred solution of 2-(4-hydroxyphenyl)-6-methoxybenzo[*b*]thiophene (1.10 g, 4.29 mmol) and 4-(2-chloroethyl)morpholine hydrochloride (3.20 g, 17.2 mmol) in anhydrous DMF (10 mL). The resultant suspension was heated in an oil bath at 75 °C for 4 h. After cooling to room temperature, the mixture was diluted with EtOAc (60 mL), washed with half-saturated aqueous NaCl solution (20 mL), dried over $MgSO_4$, filtered, and concentrated to give a solid residue. Chromatography on silica [gradient 0-15% EtOH/Et_3N (2/1) in THF/hexanes (1/1)] provided 1.43 g of the ether (90%) as a solid.

IR (KBr) 2940, 1606 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.61 (t, J = 4.6 Hz, 4H), 2.84 (t, J = 5.7 Hz, 2H), 3.76 (t, J = 4.6 Hz, 4H), 3.84 (s, 3H), 4.17 (t, J = 5.7 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 6.98 (dd, J = 8.6 and 2.2 Hz, 1H), 7.30 (d, J = 2.2 Hz, 1H), 7.35 (s, 1H), 7.60 (d, J = 8.6 Hz, 2H), 7.63 (d, J = 8.6 Hz, 1H); FDMS *m/e* 369 (M^+).

Part D. 3-Bromo-4-[(1-pyrrolidinyl)methyl]phenyl 6-Methoxy-2-[4-[2-(4-morpholinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl Ketone.



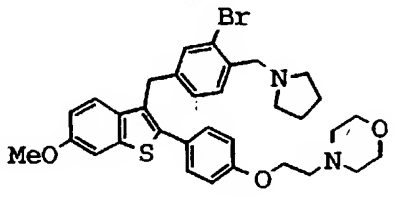
Oxalyl chloride (1.11 mL, 12.7 mmol) was added to a stirred suspension of the above benzothiophene (812 mg, 2.53 mmol) in anhydrous $ClCH_2CH_2Cl$ (6 mL), followed by the

addition of 2 drops of DMF. The suspension was stirred at room temperature under nitrogen atmosphere for 6 h, then it was concentrated to dryness under vacuum at 50 °C.

To the crude benzoyl chloride suspended in anhydrous CH_2Cl_2 (5 mL) was added a solution of the benzothiophene of Part C above (624 mg, 1.69 mmol) in anhydrous CH_2Cl_2 (10 mL). The mixture was cooled to 0 °C, treated with $AlCl_3$ (1.35 g, 10.1 mmol), and stirred for 1 h. THF (10 mL) was added to the mixture at 0 °C, followed by the slow, sequential additions of saturated aqueous $NaHCO_3$ (30 mL) and saturated aqueous Rochelle's salt solution (10 mL). Then the two-layered solution was stirred vigorously for 70 min. The organic layer was separated and the aqueous layer was extracted with EtOAc (60 mL x 2). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed on silica [gradient 0-20% EtOH/Et_3N (2/1) in THF/hexanes (1/1)] to give 695 mg (65%) of the ketone as a foam.

IR (neat) 2961, 1645, 1606 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.80 (br s, 4H), 2.52-2.57 (m, 8H), 2.76 (t, J = 5.7 Hz, 2H), 3.66 (s, 2H), 3.72-3.89 (m, 4H), 3.91 (s, 3H), 4.04 (t, J = 5.7 Hz, 2H), 6.75 (d, J = 8.7 Hz, 2H), 7.20 (dd, J = 8.9 and 2.3 Hz, 1H), 7.25-7.30 (m, 2H), 7.34 (d, J = 2.3 Hz, 1H), 7.38 (d, J = 7.9 Hz, 1H), 7.62 (dd, J = 7.9 and 1.6 Hz, 1H), 7.68 (d, J = 8.9 Hz, 1H), 7.91 (d, J = 1.6 Hz, 1H); FDMS m/e 634 (M^+, ^{79}Br) and 636(M^+, ^{81}Br).

Part E. 3-[3-Bromo-4-[(1-pyrrolidinyl)methyl]benzyl]-6-methoxy-2-[4-[2-(4-morpholinyl)ethoxy]phenyl]benzo-[*b*]thiophene.



Following the procedure of Example 34, Part D, the corresponding methylene compound was obtained as a foam in 86% yield.

IR (neat) 2958, 1608 cm^{-1}; FDMS *m/e* 621 (M+1, ^{79}Br) and 623 (M+1, ^{81}Br).

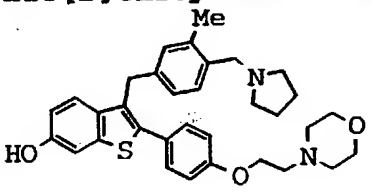
Part F. 3-[3-Bromo-4-[(1-pyrrolidinyl)methyl]benzyl]-6-hydroxy-2-[4-[2-(4-morpholinyl)ethoxy]phenyl]-benzo[*b*]thiophene Dioxalate.

Following the procedure of Example 34, Part E, the hydroxy benzothiophene salt was obtained as a white solid in 55% yield.

FDMS *m/e* 607 (M+1, ^{79}Br) and 609 (M+1, ^{81}Br).

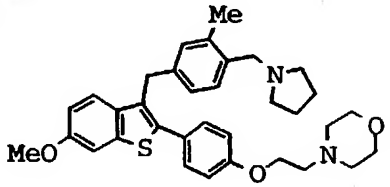
Example 38

Preparation of 6-Hydroxy-3-[3-methyl-4-[(1-pyrrolidinyl)methyl]benzyl]-2-[4-[2-(4-morpholinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



$2(C_2H_2O_4)$

Part A. 6-Methoxy-3-[3-methyl-4-[(1-pyrrolidinyl)-methyl]benzyl]-2-[4-[2-(4-morpholinyl)ethoxy]phenyl]-benzo[*b*]thiophene.



A sealed tube containing a stirred mixture of the aryl bromide of Example 37, Part E, (283 mg, 0.456 mmol), tetramethlytin (0.316 mL, 2.28 mmol), and tetrakis(triphenyl-phosphine)palladium(0) (16 mg, 0.014 mmol) in *o*-xylene (5 mL) was heated in an oil bath at 155 °C for 1 h. A black

precipitate was formed. The mixture was cooled to room temperature and subjected to chromatography on silica [gradient 0-20% EtOH/Et_3N (2/1) in THF/hexanes (1/1)] to give 94 mg (37%, low yield attributed to spill) of the corresponding aryl methyl compound as a foam.

IR (neat) 2957, 1608 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.78 (br s, 4H), 3.30 (s, 3H), 2.54-2.61 (m, 8H), 2.82 (t, J = 5.7 Hz, 2H), 3.57 (s, 2H), 3.75 (t, J = 4.5 Hz, 4H), 3.87 (s, 3H), 4.14 (t, J = 5.7 Hz, 2H), 4.18 (s, 2H), 6.88-6.96 (m, 4H), 7.18 (d, J = 7.9 Hz, 1H), 7.32-7.44 (m, 5H); FDMS *m/e* 556 (M^+).

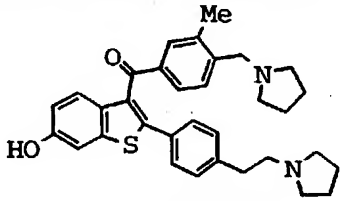
Part B. 6-Hydroxy-3-[3-methyl-4-[(1-pyrrolidinyl)-methyl]benzyl]-2-[4-[2-(4-morpholinyl)ethoxy]phenyl]-benzo[*b*]thiophene Dioxalate.

Following the procedure of Example 34, Part E, the hydroxy benzothiophene salt was obtained as a white solid in 55% yield.

IR (KBr) 3455 (br), 2970, 2840-2220 (br), 1723, 1630 (br), 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.79-1.89 (m, 4H), 2.27 (s, 3H), 2.63-2.71 (m, 4H), 2.90-3.12 (m, 6H), 3.55-3.63 (m, 4H), 4.13-4.24 (m, 6H), 6.88-7.04 (m, 5H), 7.28-7.39 (m, 5H); FDMS *m/e* 543 (M+1).

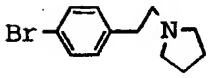
Example 39

Preparation of 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethyl]phenyl]benzo[*b*]thiophen-3-yl 3-Methyl-4-[(1-pyrrolidinyl)methyl]phenyl Ketone Dioxalate.



$2(C_2H_2O_4)$

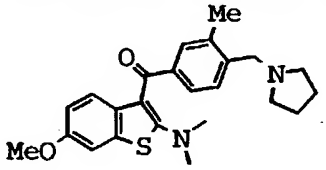
Part A. 1-Bromo-4-[2-(1-pyrrolidinyl)ethyl]benzene.



Methanesulfonyl chloride (2.12 mL, 27.4 mmol) was added to a stirred solution of 4-bromophenethyl alcohol (5.00 g, 24.9 mmol) and anhydrous pyridine (2.21 mL, 27.4 mmol) in anhydrous CH_2Cl_2 (25 mL) at 0 °C under nitrogen atmosphere. Upon the completion of the addition the mixture was allowed to stir at room temperature for 8 h. Then the reaction mixture was cooled to 0 °C and treated with pyrrolidine (10.4 mL, 124 mmol). After stirring at room temperature for 2 h, the mixture was diluted with EtOAc (120 mL), washed with half-saturated $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed on silica [gradient 0-10% EtOH/Et_3N (2/1) in THF/hexanes (1/1)] to give 5.37 g (85%) of the substituted pyrrolidine as an oil.

IR ($CHCl_3$) 2933, 1489 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (br s, 4H), 2.56 (br s, 4H), 2.64-2.80 (m, 4H), 7.10 (d, J = 7.8 Hz, 2H), 7.40 (d, J = 7.8 Hz, 2H); FDMS *m/e* 253 (M+, ^{79}Br) and 255 (M+, ^{81}Br).

Part B. 2-Dimethylamino-6-(methoxy)benzo[*b*]thiophen-3-yl 3-Methyl-4-[(1-pyrrolidinyl)methyl]phenyl Ketone.



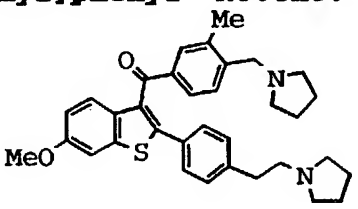
Oxalyl chloride (2.57 mL, 29.5 mmol) was added to a stirred suspension of 3-methyl-4-[(1-pyrrolidinyl)methyl]-benzoic acid hydrochloride (1.76 g, 5.90 mmol) in anhydrous $ClCH_2CH_2Cl$ (12 mL), followed by the addition of 2 drops of DMF. The suspension was stirred at room temperature under nitrogen atmosphere for 6 h, then it was concentrated to dryness under vacuum at 50 °C.

To the crude benzoyl chloride obtained and suspended in anhydrous chlorobenzene (10 mL) was added 2-dimethylamino-6-

methoxybenzo[*b*]thiophene (1.02 g, 4.92 mmol. The resultant mixture was heated in an oil bath at 110 °C for 2 h. After cooling to room temperature, the mixture was diluted with EtOAc (80 mL), washed with saturated $NaHCO_3$ (25 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed on silica [gradient 0-10% EtOH/Et_3N (2/1) in THF/hexanes (1/1)] to give 1.50 g (75%) of the ketone as a foam.

IR ($CHCl_3$) 2950, 1647, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81 (br s, 4H), 2.39 (s, 3H), 2.56 (br s, 4H), 2.89 (s, 6H), 3.65 (s, 2H), 3.83 (s, 3H), 6.80 (dd, *J* = 9.0 and 2.4 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 7.32 (d, *J* = 9.0 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 8.1 Hz, 1H), 7.69 (s, 1H); FDMS *m/e* 408 (M^+); Anal. Calcd for $C_{24}H_{28}N_2O_2S$: C, 70.56; H, 6.91; N, 6.86. Found: C, 70.75; H, 7.15; N, 6.91.

Part C. 6-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethyl]-phenyl]benzo[*b*]thiophen-3-yl 3-Methyl-4-[(1-pyrrolidinyl)methyl]phenyl Ketone.



Following the procedure of Example 34, Part C, the trisubstituted benzothiophene was obtained from the aryl bromide of Part A above and the amino benzothiophene of Part B above as a foam in 96% yield.

IR ($CHCl_3$) 2964, 1647, 1603 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75-1.82 (m, 8H) 2.25 (s, 3H), 2.44 (br s, 4H), 2.51-2.61 (m, 6H), 2.71-2.76 (m, 2H), 3.53 (s, 2H), 3.90 (s, 3H), 6.99 (dd, *J* = 8.7 and 2.1 Hz, 1H), 7.05 (d, *J* = 8.1 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.29-7.34 (m, 3H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.58 (s, 1H), 7.60 (d, *J* = 8.7 Hz, 1H); FDMS *m/e* 538 (M+); Anal. Calcd for $C_{34}H_{38}N_2O_2S$: C, 75.80; H, 7.11; N, 5.20. Found: C, 75.67; H, 7.10; N, 5.25.

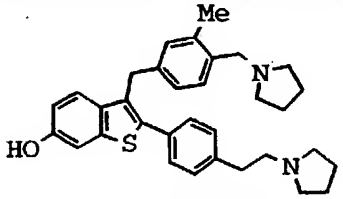
Part D. 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethyl]-phenyl]benzo[*b*]thiophen-3-yl 3-Methyl-4-[(1-pyrrolidinyl)methyl]phenyl Ketone Dioxalate.

Following the procedure of Example 34, Part E, the title compound was obtained as a yellowish solid in 77% yield.

IR (KBr) 3420 (br), 2970, 2850-2300 (br), 1721, 1641, 1607 cm^{-1}; ^1H NMR (DMSO-d_6) δ.1.83 (br s, 4H), 1.88 (br s, 4H), 2.26 (s, 3H), 2.81-2.91 (m, 6H), 3.21 (br s, 6H), 4.07 (s, 2H), 6.88 (dd, J = 8.7 and 2.1 Hz, 1H), 7.17 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.33-7.39 (m, 3H), 7.46 (d, J = 8.7 Hz, 1H), 7.54 (s, 1H); FDMS *m/e* 525 ($M^+-2C_2H_2O_4$); Anal. Calcd for $C_{33}H_{36}N_2O_2S\cdot 2C_2H_2O_4$: C, 63.05; H, 5.72; N, 3.97. Found: C, 63.24; H, 6.02; N, 4.22.

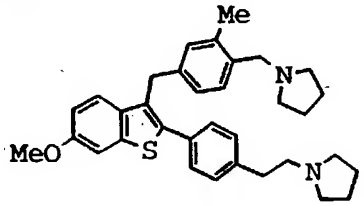
Example 40

Preparation of 6-Hydroxy-3-[3-methyl-4-[(1-pyrrolidinyl)methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethyl]-phenyl]benzo[*b*]thiophene Dioxalate.



$2(C_2H_2O_4)$

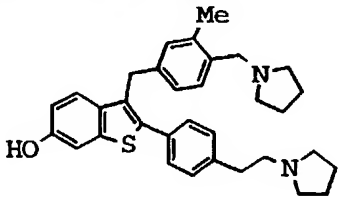
Part A. 6-Methoxy-3-[3-methyl-4-[(1-pyrrolidinyl)-ethyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethyl]phenyl]-benzo[*b*]thiophene.



Following the procedure of Example 34, Part D, the methylene compound was obtained from the ketone of Example 39, Part C, as a foam in 67% yield.

IR (KBr) 2953, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77 (br s, 4H), 1.83 (br s, 4H), 2.29 (s, 3H), 2.51 (br s, 4H), 2.60 (br s, 4H), 2.70-2.75 (m, 2H), 2.85-2.88 (m, 2H), 3.54 (s, 2H), 3.88 (s, 3H), 4.20 (s, 2H), 6.88-6.95 (m, 3H), 7.17 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 2.1 Hz, 1H), 7.38-7.45 (m, 3H); FDMS *m/e* 524 (M^+); Anal. Calcd for $C_{34}H_{40}N_2OS$: C, 77.82; H, 7.68; N, 5.34. Found: C, 78.03; H, 7.58; N, 5.54.

Part B. 6-Hydroxy-3-[3-methyl-4-[(1-pyrrolidinyl)-methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethyl]phenyl]-benzo[*b*]thiophene Dioxalate.



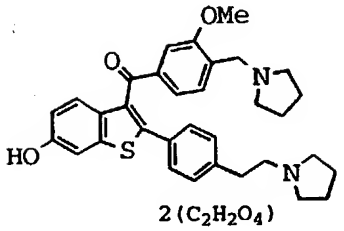
$2(C_2H_2O_4)$

Following the procedure of Example 34, Part D, the hydroxy benzothiophene salt was obtained as a white solid in 73% yield.

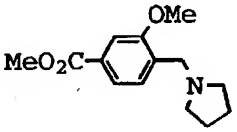
IR (KBr) 3420 (br), 2976, 2830-2230 (br), 1722, 1613 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.81-1.91 (m, 8H), 2.26 (s, 3H), 2.95-3.11 (m, 6H), 3.19-3.35 (m, 6H), 4.15 (s, 2H), 4.17 (s, 2H), 6.79 (dd, J = 8.6 and 2.0 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.99 (s, 1H), 7.26 (d, J = 2.0 Hz, 1H), 7.29-7.43 (m, 6H); FDMS *m/e* 511 ($M+1-2C_2H_2O_4$); Anal. Calcd for $C_{33}H_{38}N_2OS \cdot 2C_2H_2O_4$: C, 64.33; H, 6.13; N, 4.06. Found: C, 64.42; H, 6.40; N, 4.11.

Example 41

Preparation of 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethyl]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)methyl]phenyl Ketone Dioxalate.



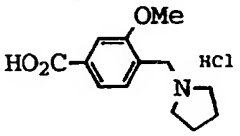
Part A. Methyl 3-Methoxy-4-[(1-pyrrolidinyl)methyl]-benzoate.



Following the procedure of Example 37, Part A, the substituted pyrrolidine was obtained from methyl 3-methoxy-4-methylbenzoate as an oil in 65% yield.

IR ($CHCl_3$) 2954, 1716 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (br s, 4H), 2.89 (br s, 4H), 3.91 (s, 3H), 3.92 (s, 3H), 3.98 (br t, J = 6.8 Hz, 2H), 7.56 (s, 1H), 7.61-7.67 (m, 2H); FDMS *m/e* 249 (M+).

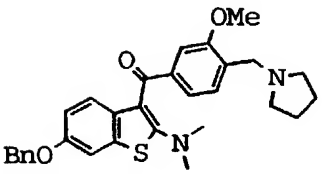
Part B. 3-Methoxy-4-[(1-pyrrolidinyl)methyl]benzoic Acid Hydrochloride.



Following the procedure of Example 37, Part B, the acid was obtained from the above ester as a yellowish solid in 65% crude yield.

^1H NMR (DMSO-d_6) δ1.89-1.94 (br s, 4H), 3.01-3.05 (br s, 2H), 3.26-3.34 (br s, 2H), 3.88 (s, 3H), 4.32 (s, 2H), 7.53 (s, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 7.7 Hz, 1H); FDMS *m/e* 235 (M+).

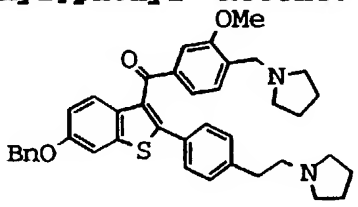
Part C. 6-Benzyloxy-2-(dimethylamino)benzo[b]thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)methyl]phenyl Ketone.



Following the procedure of Example 39, Part B, the ketone was obtained from the above acid and 6-benzyloxy-2-dimethylaminobenzo[*b*]thiophene as a foam in 81% yield.

IR ($CHCl_3$) 2970, 1621, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (br s, 4H), 2.70 (br s, 4H), 2.89 (s, 6H), 3.80 (s, 2H), 3.88 (s, 3H), 5.08 (s, 2H), 6.89 (dd, *J* = 8.9 and 2.5 Hz, 1H), 7.20 (d, *J* = 2.3 Hz, 1H), 7.33-7.47 (m, 9H); FDMS *m/e* 500 (M^+).

Part D. 6-Benzyloxy-2-[4-[2-(1-pyrrolidinyl)ethyl]-phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)methyl]phenyl Ketone.



Following the procedure of Example 34, Part C, the trisubstituted benzothiophene was obtained from the dimethylamino compound of Part C as a foam in 81% yield.

IR ($CHCl_3$) 2965, 1648, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77-1.82 (m, 8H), 2.52 (br s, 4H), 2.60 (br s, 4H), 2.61-2.67 (m, 2H), 2.75-2.80 (m, 2H), 3.63 (s, 2H), 3.80 (s, 3H), 5.16 (s, 2H), 7.06 (d, *J* = 8.1 Hz, 2 + 1H superimposed), 7.25-7.50 (m, 11H), 7.61 (d, *J* = 8.9 Hz, 1H); FDMS *m/e* 631 (M+1).

Part E. 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethyl]-phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)methyl]phenyl Ketone Dioxalate.

To a stirred solution of the above benzyloxy benzothiophene (440 mg, 0.698 mmol) in THF (8 mL) under nitrogen atmosphere were sequentially added 10% Pd/C (440 mg)

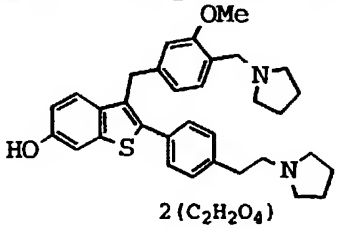
and 25% aqueous HCO_2NH_4 (2 mL). The resultant mixture was stirred under a balloon nitrogen atmosphere for 7 h. After filtration, the filtrate was diluted with EtOAc (50 mL), washed with half-saturated NaCl (15 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed on silica [gradient 0-20% EtOH/TEA (2/1) in THF/hexanes (1/1)] to give 225 mg (60%) of the hydroxy benzothiophene as a foam.

A solution of oxalic acid (64.2 mg, 0.712 mmol) in EtOAc (6 mL) was added dropwise to a stirred solution of the hydroxy benzothiophene (175 mg, 0.323 mmol) in THF (4 mL). The resultant white suspension was filtered and the white solid was dried at 60 °C under vacuum to provide 213 mg (91%) of the corresponding dioxalate.

IR (neat) 3450 (br), 2964, 2830-2220, 1719, 1640, 1607 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.83-1.88 (br s, 8H), 2.83-2.93 (m, 6H), 3.18 (br s, 6H), 3.75 (s, 3H), 4.06 (s, 2H), 6.90 (dd, J = 8.8 and 2.2 Hz, 1H), 7.15-7.39 (m, 8H), 7.43 (d, J = 8.8 Hz, 1H); FDMS *m/e* 541 (M+1-$2C_2H_2O_4$); Anal. Calcd for $C_{33}H_{36}N_2O_3S \cdot 2C_2H_2O_4$: C, 61.66; H, 5.59; N, 3.89. Found: C, 61.91; H, 5.69; N, 4.00.

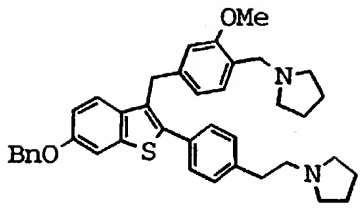
Example 42

Preparation of 6-Hydroxy-3-[3-methoxy-4-[(1-pyrrolidinyl)methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethyl]phenyl]benzo[*b*]thiophene Dioxalate.



$2(C_2H_2O_4)$

Part A. 6-Benzyloxy-3-[3-methoxy-4-[(1-pyrrolidinyl)-methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethyl]phenyl]-benzo[*b*]thiophene.



Following the procedure of Example 34, Part D, the methylene compound was obtained from the ketone of Example 41, Part D as a foam in 62% yield.

IR ($CHCl_3$) 2966, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82 (br s, 8H), 2.60 (br s, 8H), 2.68-2.75 (m, 2H), 2.72-2.95 (m, 2H), 3.68 (s, 5H, OCH_3 and CH_2), 4.22 (s, 2H), 5.13 (s, 2H), 6.64 (s, 1H), 6.71 (d, *J* = 7.5 Hz, 1H), 6.98 (dd, *J* = 8.5 and 2.0 Hz, 1H), 7.23 (br s, 2H), 7.30-7.50 (m, 10H); FDMS *m/e* 616 (M^+). Anal. Calcd for $C_{40}H_{44}N_2O_2S$: C, 77.88; H, 7.19; N, 4.54. Found: C, 77.93; H, 7.22; N, 4.61.

Part B. 6-Hydroxy-3-[3-methoxy-4-[(1-pyrrolidinyl)-methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethyl]phenyl]-benzo[*b*]thiophene Dioxalate.

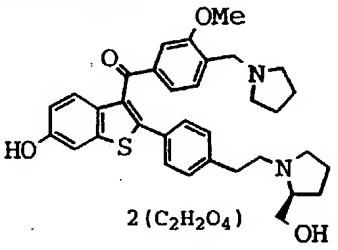
Following the procedure of Example 41, Part E, the title hydroxy benzothiophene salt was obtained from the benzyl ether as a white solid in an overall 65% yield.

IR (KBr) 3420 (br), 2980, 2830-2240 (br), 1720, 1613 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.86-1.93 (m, 8H), 2.96-3.01 (m, 2H), 3.06-3.21 (m, 4H), 3.25-3.50 (m, 6H), 3.70 (s, 3H), 4.14 (s, 2H), 4.20 (s, 2H), 6.60 (d, *J* = 7.9 Hz, 1H), 6.81 (dd, *J* = 8.7 and 2.1 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 2 + 1H superimposed), 7.36 (d, *J* = 8.2 Hz, 2H) 7.42-7.46 (m, 3H); FDMS *m/e* 527 (M+1-$2C_2H_2O_4$); Anal. Calcd for $C_{33}H_{38}N_2O_2S \cdot 1.7C_2H_2O_4$: C, 64.31; H, 6.14; N, 4.12. Found: C, 64.25; H, 6.42; N, 4.02.

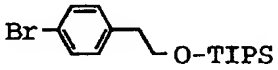
Example 43

Preparation of 6-Hydroxy-2-[4-[2-[1-[(*S*)-2-hydroxymethyl]pyrrolidinyl]ethyl]phenyl]benzo[*b*]-

thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)methyl]-phenyl Ketone Dioxalate.



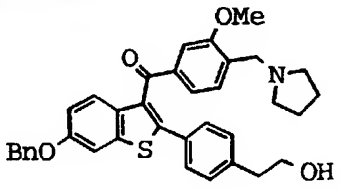
Part A. 1-Bromo-4-[2-(triisopropylsilyloxy)ethyl]-benzene.



Triisopropylsilyl trifluoromethanesulfonate (35.1 mL, 130 mmol) was added to a stirred solution of 4-bromophenethyl alcohol (20.2 g, 100 mmol) and anhydrous triethylamine (27.8 mL, 200 mmol) in anhydrous CH_2Cl_2 (200 mL) at room temperature under nitrogen atmosphere. The resultant mixture was stirred for 3 h. After dilution with EtOAc (200 mL), the mixture was washed with a mixed aqeous solution of saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed on silica (gradient 0-10% EtOAc in hexanes) to give 33.5 g (94%) of the silyl ether as an oil.

IR ($CHCl_3$) 2944, 1489 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.03 (br s, 3H), 1.39 (br s, 18H), 2.81 (t, J = 6.8 Hz, 2H), 3.86 (t, J = 6.8 Hz, 2H), 7.11 (d, J = 8.2 Hz, 2H), 7.40 (d, J = 8.2 Hz, 2H); FDMS *m/e* 356 (M^+, ^{79}Br) and 358 (M^+, ^{81}Br).

Part B. 6-Benzyloxy-2-[4-(2-hydroxyethyl)phenyl]-benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)-methyl]phenyl Ketone.

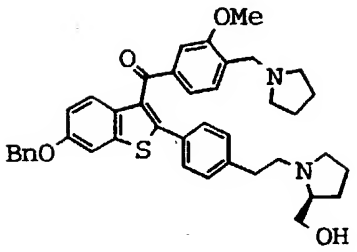


The above silyl ether (571 mg, 1.60 mmol) was added to a stirred suspension of magnesium ribbons (36.4 mg, 1.50 mmol) in anhydrous THF (2 mL) under argon atmosphere, followed by the addition of a small iodine crystal. The mixture was heated in an oil bath at 60-65 °C for 2 h to form a homogeneous Grignard solution. The Grignard solution was cooled to room temperature before it was added to a stirred solution of the compound of Example 41, Part C (500 mg, 1.00 mmol) in anhydrous THF (4 mL) at 0 °C under argon atmosphere. The resultant mixture was stirred at 0 °C for 1.5 h, then quenched with saturated aqueous NH_4Cl (5 mL). After extraction with EtOAc (25 mL x 2), the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to give a gummy residue (597 mg).

The residue was dissolved in anhydrous THF (5 mL) and treated with tetrabutylammonium fluoride (1.20 mL, 1 M in THF) at room temperature under nitrogen atmosphere. After stirring for 1.5 h, the mixture was concentrated under vacuum and chromatographed on silica [gradient 0-30% EtOH/Et_3N (2/1) in THF/hexanes (1/1)] to give 395 mg (68%) of the alcohol as a foam.

IR ($CHCl_3$) 2960, 1646, 1601 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (br s, 4H), 2.54 (br s, 4H), 2.75 (t, J = 6.2 Hz, 2H), 3.59 (s, 2H), 3.74 (t, J = 6.2 Hz, 2H), 3.79 (s, 3H), 5.18 (s, 2H), 7.05 (d, J = 8.1 Hz, 1H), 7.09-7.50 (m, 13H), 7.74 (d, J = 8.9 Hz, 1H); FDMS *m/e* 578 (M+1); Anal. Calcd for $C_{36}H_{35}NO_4S$: C, 74.84; H, 6.11; N, 2.42. Found: C, 75.02; H, 6.34; N, 2.50.

Part C. 6-Benzyloxy-2-[4-[2-[1-[(*S*)-2-hydroxymethyl]-pyrrolidinyl]ethyl]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)methyl]phenyl Ketone.



Methanesulfonyl chloride (0.420 mL, 5.43 mmol) was added to a stirred solution of the above alcohol (2.09 g, 3.62 mmol) in anhydrous pyridine (5 mL) at 0 °C under nitrogen atmosphere, and the reaction mixture was allowed to stir at room temperature for 2 h. (*S*)-Prolinol (1.25 mL, 12.7 mmol) was added and the resultant mixture was heated at 70 °C for 2 h. After dilution with EtOAc (120 mL), the mixture was washed with half-saturated $NaHCO_3$ (30 mL), dried over $MgSO_4$, filtered, concentrated, and chromatographed on silica [gradient 0-25% EtOH/Et_3N (2/1) in THF/hexanes (1/1)] to give 2.01 g (84%) of the substituted pyrrolidine a foam.

IR (neat) 3355 (br), 2958, 1646, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63-2.19 (m, 8H), 2.25-2.80 (m, 8H), 2.87 (t, *J* = 7.7 Hz, 2H), 3.15-3.58 (m, 4H), 3.44 (dd, *J* = 11.5 and 3.6 Hz, 1H), 3.60 (dd, *J* = 11.5 and 3.6 Hz, 1H), 3.62 (s, 2H), 3.80 (s, 3H), 7.04-7.08 (m, 3H), 7.23-7.47 (m, 11H), 7.62 (d, *J* = 9.0 Hz, 1H); FDMS *m/e* 661 (M+1).

Part D. 6-Hydroxy-2-[4-[2-[1-[(*S*)-2-hydroxymethyl]-pyrrolidinyl]ethyl]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(1-pyrrolidinyl)methyl]phenyl Ketone Dioxalate.

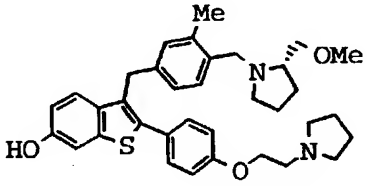
Following the procedure of Example 41-E, the title salt was obtained from the above methoxy benzothiophene as a yellowish solid in an overall 6% yield. The free base of the title compound was unstable.

^1H NMR (CD_3OD) δ 1.75-2.25 (m, 8H), 2.82-3.05 (m, 2H), 3.15-3.23 (m, 4H), 3.38-3.91 (m, 6H), 3.80 (s, 3H), 4.01-4.13 (m,

1H), 4.28 (s, 2H), 6.92 (br d, J = 6.3 Hz, 1H), 7.03-7.37 (m, 8H), 7.56 (m,1H); FDMS m/e 571 (M+1).

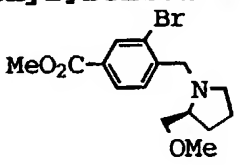
Example 44

Preparation of 6-Hydroxy-3-[3-methyl-4-[[1-[(*S*)-2-methoxymethyl]pyrrolidinyl]methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[b]thiophene Dioxalate.



$2(C_2H_2O_4)$

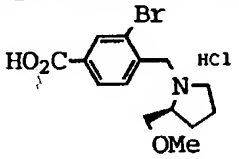
Part A. Methyl 3-Bromo-4-[[1-[(*S*)-2-methoxymethyl]-pyrrolidinyl]methyl]benzoate.



Following the procedure of Example 37, Part A, the substituted pyrrolidine was obtained from methyl 3-bromo-4-methylbenzoate and (*S*)-2-(methoxymethyl)pyrrolidine as an oil in 63% yield.

IR (neat) 2950, 1727 cm^{-1}; FDMS m/e 341 (M^+, ^{79}Br) and 343 (M^+, ^{81}Br); Anal. Calcd for $C_{15}H_{20}BrNO_3$: C, 52.64; H, 5.89; N, 4.09. Found: C, 52.91; H, 5.93; N, 3.85.

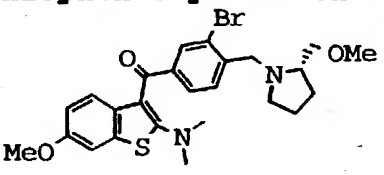
Part B. 3-Bromo-4-[[1-[(*S*)-2-methoxymethyl]-pyrrolidinyl]methyl]benzoic acid hydrochloride.



Following the procedure of Example 37, Part B, the acid was obtained from the above ester as a white solid in 100% yield.

^{1}H NMR (DMSO-d_6) δ 1.60-1.78 (m, 1H), 1.80-2.05 (m, 2H), 2.08-2.22 (m, 1H), 3.10-3.50 (m, 2H), 3.29 (s, 3H), 3.60-3.65 (m, 1H), 3.75-3.95 (m, 2H), 4.46 (br d, J = 13.4 Hz, 1H), 4.76 (d, J = 13.4 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H), 11.15 (br s, 1H), 13.55 (br s,1H).

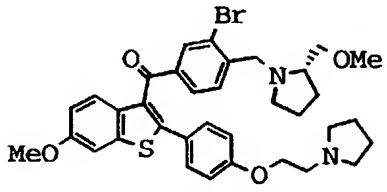
Part C. 3-Bromo-4-[[1-[(*S*)-2-methoxymethyl]-pyrrolidinyl]methyl]phenyl 2-Dimethylamino-6-methoxybenzo[*b*]thiophen-3-yl Ketone.



Following the procedure of Example 39, Part B, the ketone was obtained from the above acid as a foam in 75% yield.

IR (neat) 1626, 1544 cm^{-1}; FDMS *m/e* 516 (M^+, ^{79}Br) and 518 (M^+, ^{81}Br); Anal. Calcd for $C_{25}H_{29}BrN_2O_3S$: C, 58.03; H, 5.65; N, 5.41. Found: C, 58.15; H, 5.40; N, 5.29.

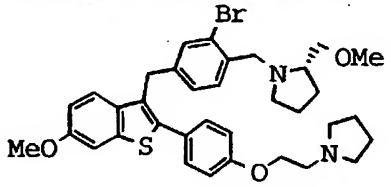
Part D. 3-Bromo-4-[[1-[(*S*)-2-methoxymethyl]-pyrrolidinyl]methyl]phenyl 6-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone.



Following the procedure of Example 34, Part C, the trisubstituted benzothiophene was obtained from the above benzothiophene and the corresponding aryl bromide as a foam in 95% yield.

IR (neat) 2962, 1645, 1606 cm^{-1}; FDMS *m/e* 662 (M^+, ^{79}Br) and 664 (M^+, ^{81}Br); Anal. Calcd for $C_{35}H_{39}BrN_2O_4S$: C, 63.34; H, 5.92; N, 4.22. Found: C, 63.18; H, 5.84; N, 4.44.

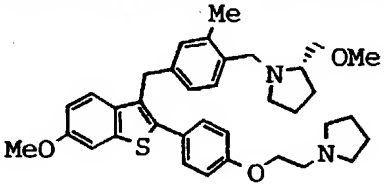
Part E. 3-[3-Bromo-4-[[1-[(*S*)-2-methoxymethyl]-pyrrolidinyl]methyl]benzyl]-6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene.



Following the procedure of Example 34, Part D, the methylene compound was obtained from the above ketone as a foam in 79% yield.

IR (neat) 2963, 1607 cm^{-1}; FDMS *m/e* 648 (M^+, ^{79}Br) and 650 (M^+, ^{81}Br); Anal. Calcd for $C_{35}H_{41}BrN_2O_3S$: C, 64.71; H, 6.36; N, 4.31. Found: C, 64.93; H, 6.42; N, 4.35.

Part F. 6-Methoxy-3-[3-methyl-4-[[1-[(*S*)-2-methoxymethyl]pyrrolidinyl]methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene.



Following the procedure of Example 38, Part A, the aryl methyl compound was obtained from the above aryl bromide as a foam in 85% yield.

IR (neat) 2962, 1608 cm^{-1}; FDMS *m/e* 584 (M^+) and 585 (M+1); Anal. Calcd for $C_{36}H_{44}N_2O_3S$: C, 73.94; H, 7.58; N, 4.79. Found: C, 73.84; H, 7.42; N, 4.50.

Part G. 6-Hydroxy-3-[3-methyl-4-[[1-[(*S*)-2-methoxymethyl]pyrrolidinyl]methyl]benzyl]-2-[4-[2-(1-

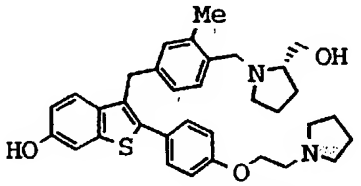
pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

Following the procedure of Example 34, Part D, a mixture of the free bases of the compounds of this example and the following example were obtained from the above dimethoxy compound. Following conversion to the dioxalate, the title compound was obtained as a white solid in a 2-step yield of 19%.

IR (KBr) 3450-2500 (br), 1718, 1609 cm^{-1}; FDMS *m/e* 571 (M+1-$2C_2H_2O_4$); Anal. Calcd for $C_{35}H_{42}N_2O_3S \cdot 2C_2H_2O_4$: C, 62.39; H, 6.18; N, 3.73. Found: C, 62.61; H, 6.02; N, 3.72.

Example 45

Preparation of 6-Hydroxy-3-[3-methyl-4-[[1-[(*S*)-2-hydroxymethyl]pyrrolidinyl]methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



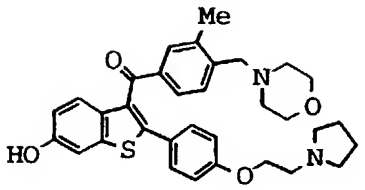
$2(C_2H_2O_4)$

Following separation of the free base in Part G of the above example, the dihydroxy compound was converted into the title dioxalate which was obtained in a white solid in a 2-step yield of 33%.

IR (KBr) 3400-2500 (br), 1721, 1609 cm^{-1}; FDMS *m/e* 557 (M+1-$2C_2H_2O_4$); Anal. Calcd for $C_{34}H_{40}N_2O_3S \cdot 1.6C_2H_2O_4$: C, 62.39; H, 6.18; N, 3.73. Found: C, 62.61; H, 6.02; N, 3.72.

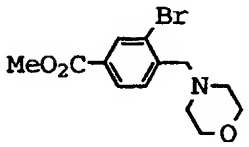
Example 46

Preparation of 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Methyl-4-[(4-morpholinyl)methyl]phenyl Ketone Dioxalate.



$2(C_2H_2O_4)$

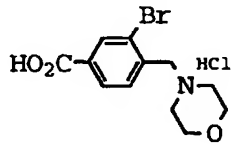
Part A. Methyl 3-Bromo-4-[(4-morpholinyl)methyl]-benzoate.



Following the procedure of Example 37, Part A, the substituted morpholine was obtained from methyl 3-bromo-4-methylbenzoate and morpholine as an oil in 53% yield.

IR (neat) 2953, 1727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48-2.60 (m, 4H), 3.63 (s, 2H), 3.70-3.80 (m, 4H), 3.93 (s, 3H), 7.59 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 8.23 (s, 1H); FDMS m/e 313 (M^+,^{79}Br) and 315 (M^+,^{81}Br); Anal. Calcd for $C_{13}H_{16}BrNO_3$: C, 49.70; H, 5.13; N, 4.46. Found: C, 49.42; H, 4.98; N, 4.55.

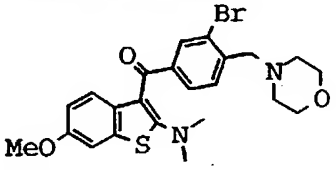
Part B. 3-Bromo-4-[(4-morpholinyl)methyl]benzoic Acid Hydrochloride.



Following the procedure of Example 37, Part B, the acid was obtained from the above ester as a white solid in 100% yield.

^1H NMR (DMSO-d_6) δ 3.25 (br s, 4H), 3.88 (br s, 4H), 4.51 (s, 2H), 7.93 (d, J = 8.0 Hz, 1H), 8.12 (s, 1H), 8.19 (br d, J = 8.0 Hz, 1H).

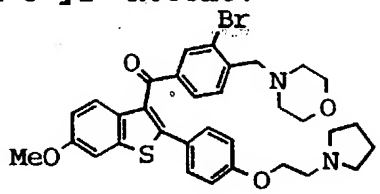
Part C. 3-Bromo-4-[(4-morpholinyl)methyl]phenyl 2-Dimethylamino-6-methoxybenzo[*b*]thiophen-3-yl Ketone.



Following the procedure of Example 39, Part C, the ketone was obtained from 2-dimethylamino-6-methoxybenzo[*b*]thiophene and the above acid as a foam in 80% yield.

IR (neat) 1622, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.52-2.60 (m, 4H), 2.89 (s, 6H), 3.65 (s, 2H), 3.72-3.80 (m, 4H), 3.83 (s, 3H), 6.84 (dd, *J* = 8.9 and 2.4 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.39 (d, *J* = 8.9 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.77 (dd, *J* = 8.0 and 1.4 Hz, 1H), 8.05 (d, *J* = 1.4 Hz, 1H); FDMS *m/e* 488 (M^+,^{79}Br) and 490 (M^+,^{81}Br).

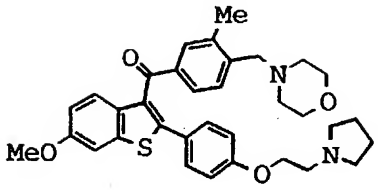
Part D. 3-Bromo-4-[(4-morpholinyl)methyl]phenyl 6-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl Ketone.



Following the procedure of Example 34, Part C, the trisubstituted benzothiophene was obtained from the corresponding aryl bromide and the above benzothiophene as a foam in 80% yield.

IR (neat) 2959, 1622, 1598 cm^{-1}; FDMS *m/e* 635 (M+1, ^{79}Br) and 637 (M+1, ^{79}Br).

Part E. 6-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 3-Methyl-4-[(4-morpholinyl)methyl]phenyl Ketone.



Following the procedure of Example 34, Part E, the aryl methyl compound was obtained from the above aryl bromide as a foam in 76% yield.

IR (neat) 2958, 1643, 1603 cm^{-1}; FDMS *m/e* 570 (M^+).

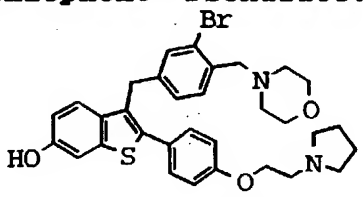
Part F. 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 3-Methyl-4-[(4-morpholinyl)methyl]phenyl, Ketone Dioxalate.

Following the procedure of Example 34, Part E, the salt of the hydroxy benzothiophene was obtained from the above methoxy benzothiophene as a yellowish solid in a 2-step yield of 69%.

IR (KBr) 3400-2500 (br), 1725, 1639 cm^{-1}; FDMS *m/e* 557(M+1-$2C_2H_2O_4$); Anal. Calcd for $C_{33}H_{36}N_2O_4S \cdot 2C_2H_2O_4$: C, 60.32; H, 5.47; N, 3.80. Found: C, 60.60; H, 5.53; N, 4.01.

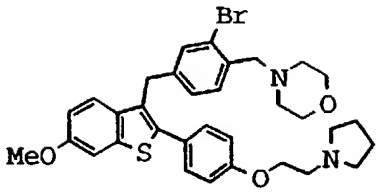
Example 47

Preparation of 3-[3-Bromo-4-[(4-morpholinyl)methyl]-benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene Dioxalate.



$2(C_2H_2O_4)$

Part A. 3-[3-Bromo-4-[(4-morpholinyl)methyl]benzyl]-6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophene.



Following the procedure of Example 34, Part D, the methylene compound was obtained from the ketone of Example 46, Part A as a foam in 84% yield.

IR (neat) 2958, 1608 cm^{-1}; FDMS *m/e* 621 (M+1,^{79}Br) and 623 (M+1,^{81}Br); Anal. Calcd for $C_{33}H_{37}BrN_2O_3S$: C, 63.76; H, 6.00; N, 4.51. Found: C, 63.50; H, 5.82; N, 4.38.

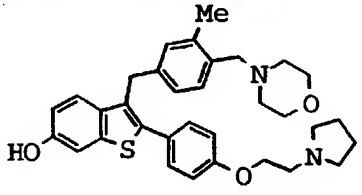
Part B. 3-[3-Bromo-4-[(4-morpholinyl)methyl]benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophene Dioxalate.

Following the procedure of Example 34, Part E, the title hydroxy benzothiophene salt was obtained from the above methoxy benzothiophene as a white solid in 66% yield.

IR (KBr) 3400-2500 (br), 1721, 1607 cm^{-1}; FDMS *m/e* 607 (M+1-$2C_2H_2O_4$,^{79}Br) and 609 (M+1-$2C_2H_2O_4$,^{81}Br); Anal. Calcd for $C_{32}H_{35}BrN_2O_3S \cdot 1.5C_2H_2O_4$: C, 56.61; H, 5.16; N, 3.77. Found: C, 56.70; H, 5.13; N, 3.95.

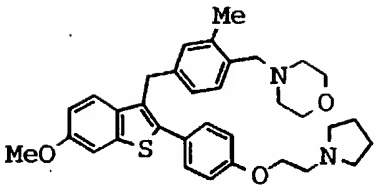
Example 48

Preparation of 6-Hydroxy-3-[3-methyl-4-[(4-morpholinyl)methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



$2(C_2H_2O_4)$

Part A. 6-Methoxy-3-[3-methyl-4-[(4-morpholinyl)-methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene.



Following the procedure of Example 38, Part A, the aryl methyl compound was obtained from the aryl bromide of Example 47, Part A as a foam in 91% yield.

IR (neat) 2957, 1608 cm^{-1}; FDMS *m/e* 556 (M^+).

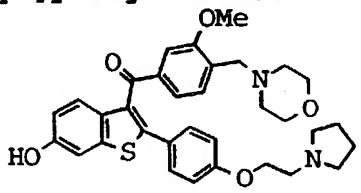
Part B. 6-Hydroxy-3-[3-methyl-4-[(4-morpholinyl)-methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene Dioxalate.

Following the procedure of Example 34, Part E, the title hydroxy benzothiophene salt was obtained from the above methoxy benzothiophene as a white solid in a 2-step yield of 79%.

IR (KBr) 3400-2500 (br), 1722, 1610 cm^{-1}; FDMS *m/e* 543 (M^+-$2C_2H_2O_4$); Anal. Calcd for $C_{33}H_{38}N_2O_3S \cdot 1.5C_2H_2O_4$: C, 63.79; H, 6.10; N, 4.13. Found: C, 63.92; H, 6.15; N, 4.31.

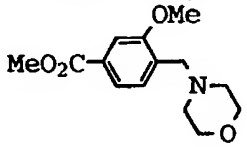
Example 49

Preparation of 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(4-morpholinyl)methyl]phenyl Ketone Dioxalate.



$2(C_2H_2O_4)$

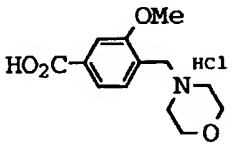
Part A. Methyl 3-Methoxy-4-(4-morpholinyl)benzoate.



Following the procedure of Example 37, Part A, the substituted morpholine was obtained from methyl 4-methyl-3-methoxybenzoate and morpholine as an oil in 79% yield.

IR (neat) 2953, 1723, 1582 cm^{-1}; FDMS *m/e* 265 (M^+); Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.11; H, 7.20; N, 5.50.

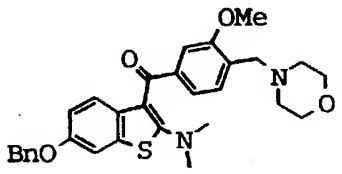
Part B. 3-Methoxy-4-(4-morpholinyl)benzoic Acid Hydrochloride.



Following the procedure of Example 37, Part B, the acid was obtained from the ester as a white solid in 100% yield.

^1H NMR (DMSO-d_6) δ 3.05 (br s, 2H), 3.15-3.25 (m, 2H), 3.85 (s, 2H), 3.87 (s, 5H, OCH_3 and CH_2), 4.29 (s, 2H), 7.52 (s, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 11.65 (br s, 1H), 13.15 (br s, 1H).

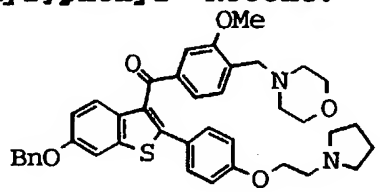
Part C. 6-Benzyloxy-2-(dimethylamino)benzo[*b*]-thiophen-3-yl 3-Methoxy-4-[(4-morpholinyl)methyl]-phenyl Ketone.



Following the procedure of Example 39, Part B, the ketone was obtained from 6-benzyloxy-2-(dimethylamino)-benzo[*b*]thiophene and the above acid as a foam in 81% yield.

IR (neat) 2954, 1625, 1600 cm^{-1}; FDMS *m/e* 516 (M^+); Anal. Calcd for $C_{30}H_{32}N_2O_4S$: C, 69.74; H, 6.24; N, 5.42. Found: C, 70.03; H, 6.47; N, 5.44.

Part D. 6-Benzyloxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(4-morpholinyl)methyl]phenyl Ketone.



Following the procedure of Example 34, Part C, the trisubstituted benzothiophene was obtained from the corresponding aryl bromide and the above benzothiophene as a foam in 88% yield.

IR (neat) 2961, 1651 cm^{-1}; FDMS *m/e* 662 (M^+) and 663 (M+1); Anal. Calcd for $C_{40}H_{42}N_2O_5S$: C, 72.48; H, 6.39; N, 4.23. Found: C, 72.47; H, 6.35; N, 4.43.

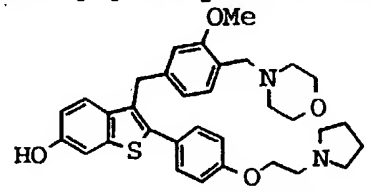
Part E. 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(4-morpholinyl)methyl]phenyl Ketone Dioxalate.

Following the procedure of Example 41, Part E, the salt of the hydroxy benzothiophene was obtained from the above benzyl ether as a yellowish solid in an overall 74% yield.

IR (KBr) 3400-2500 (br), 1722, 1633, 1606 cm^{-1}; FDMS *m/e* 573 (M+1-$2C_2H_2O_4$); Anal. Calcd for $C_{33}H_{36}N_2O_5S \cdot 2.3C_2H_2O_4$: C, 57.91; H, 5.25; N, 3.59. Found: C, 57.93; H, 5.37; N, 3.78.

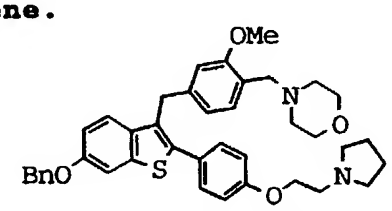
Example 50

Preparation of 6-Hydroxy-3-[3-methoxy-4-[(4-morpholinyl)methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



$2(C_2H_2O_4)$

Part A. 6-Benzyloxy-3-[3-methoxy-4-[(4-morpholinyl)-methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophene.



Following the procedure of Example 34, Part D, the methylene compound was obtained from the ketone of Example 49, Part D as a foam in 82% yield.

IR (neat) 2961, 1609 cm^{-1}; FDMS *m/e* 649 (M+1); Anal. Calcd for $C_{40}H_{44}N_2O_4S$: C, 74.04; H, 6.84; N, 4.32. Found: C, 74.30; H, 7.18; N, 4.34.

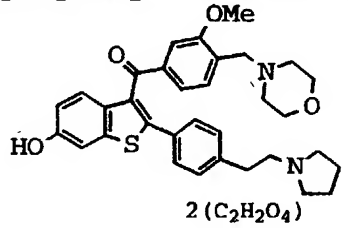
Part B. 6-Hydroxy-3-[3-methoxy-4-[(4-morpholinyl)-methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophene Dioxalate.

Following the procedure of Example 41, Part E, the salt of the hydroxy benzothiophene was obtained from the above benzyl ether as a white solid in an overall 90% yield.

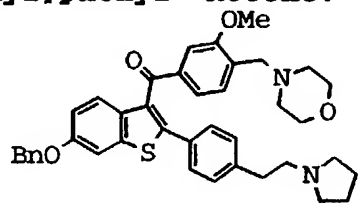
IR (KBr) 3400-2500 (br), 1613 cm^{-1}; FDMS *m/e* 559 (M+1-$2C_2H_2O_4$); Anal. Calcd for $C_{33}H_{38}N_2O_4S \cdot 1.4C_2H_2O_4$: C, 62.79; H, 6.01; N, 4.09. Found: C, 62.73; H, 5.93; N, 4.04.

Example 51

Preparation of 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethyl]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(4-morpholinyl)methyl]phenyl Ketone Dioxalate.



Part A. 6-Benzyloxy-2-[4-[2-(1-pyrrolidinyl)ethyl]-phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(4-morpholinyl)methyl]phenyl Ketone.



Following the procedure of Example 34, Part C, the trisubstituted benzothiophene was obtained from the aryl bromide of Example 39, Part A and the ketone of Example 49, Part C as a foam in 91% yield.

IR (neat) 3400 (br), 2959, 1651, 1600 cm^{-1}; FDMS *m/e* 646 (M^+); Anal. Calcd for $C_{40}H_{42}N_2O_4S$: C, 74.27; H, 6.54; N, 4.33. Found: C, 74.09; H, 6.74; N, 4.38.

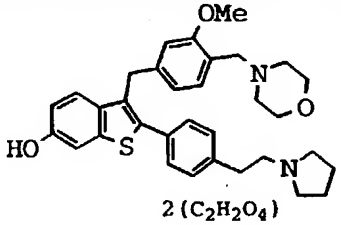
Part B. 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethyl]-phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(4-morpholinyl)methyl]phenyl Ketone Dioxalate.

Following the procedure of Example 41, Part E, the salt of the hydroxy benzothiophene was obtained from the above benzyl ether as a yellowish solid in an overall 83% yield.

IR (KBr) 3400-2500 (br), 1718, 1645 cm^{-1}; FDMS *m/e* 557 (M+1-$2C_2H_2O_4$); Anal. Calcd for $C_{33}H_{36}N_2O_4S \cdot 2C_2H_2O_4$: C, 60.32; H, 5.47; N, 3.80. Found: C, 60.06; H, 5.43; N, 4.00.

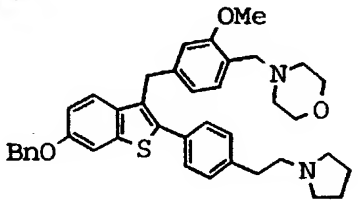
Example 52

Preparation of 6-Hydroxy-3-[3-methoxy-4-[(4-morpholinyl)methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethyl]phenyl]benzo[*b*]thiophene Dioxalate.



$2(C_2H_2O_4)$

Part A. 6-Benzyloxy-3-[3-methoxy-4-[(4-morpholinyl)-methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethyl]phenyl]-benzo[*b*]thiophene.



Following the procedure of Example 34, Part D, the methylene compound was obtained from the ketone of Example 51, Part A as a foam in 100% yield.

IR (neat) 2957, 1600 cm^{-1}; FDMS *m/e* 632 (M^+); Anal. Calcd for $C_{40}H_{44}N_2O_3S$: C, 75.92; H, 7.01; N, 4.43. Found: C, 75.93; H, 7.00; N, 4.39.

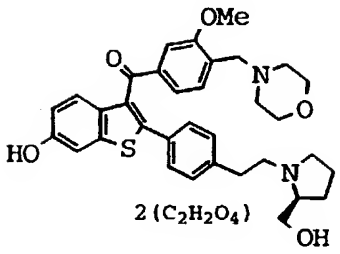
Part B. 6-Hydroxy-3-[3-methoxy-4-[(4-morpholinyl)-methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethyl]phenyl]-benzo[*b*]thiophene Dioxalate.

Following the procedure of Example 41, Part E, the salt of the hydroxy benzothiophene was obtained from the above benzyl ether as a white solid in an overall 83% yield.

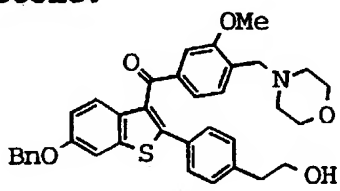
IR (KBr) 3400-2500 (br), 1719, 1612 cm^{-1}; FDMS *m/e* 543 (M+1-$2C_2H_2O_4$); Anal. Calcd for $C_{33}H_{38}N_2O_3S \cdot 1.7C_2H_2O_4$: C, 62.83; H, 6.00; N, 4.03. Found: C, 62.72; H, 6.05; N, 4.16.

Example 53

Preparation of 6-Hydroxy-2-[4-[2-[1-[(*S*)-2-hydroxymethyl]pyrrolidinyl]ethyl]phenyl]benzo[*b*]-thiophen-3-yl 3-Methoxy-4-[(4-morpholinyl)methyl]-phenyl Ketone Dioxalate.



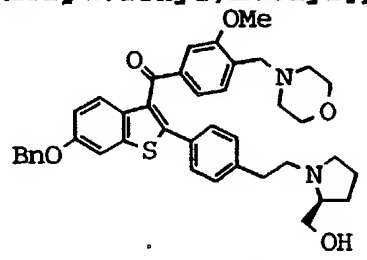
Part A. 6-Benzyloxy-2-[4-(2-hydroxyethyl)phenyl]-benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(4-morpholinyl)-methyl]phenyl Ketone.



Following the procedure of Example 43, Part A, the trisubstituted benzothiophene was obtained from the ketone of Example 49, Part C as a foam in an overall 95% yield.

IR (neat) 3424 (br), 2936, 1647, 1600 cm^{-1}; FDMS *m/e* 593 (M^+); Anal. Calcd for $C_{36}H_{35}NO_5S$: C, 72.83; H, 5.94; N, 2.36. Found: C, 72.66; H, 5.95; N, 2.59.

Part B. 6-Benzyloxy-2-[4-[2-[1-[(*S*)-2-hydroxymethyl]-pyrrolidinyl]ethyl]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(4-morpholinyl)methyl]phenyl Ketone.



Following the procedure of Example 43, Part B, the substituted prolinol was obtained from the above alcohol and (*S*)-prolinol as a foam in an overall 43% yield.

IR (neat) 3389 (br), 2954, 1654, 1600 cm^{-1}; FDMS *m/e* 677 (M+1); Anal. Calcd for $C_{41}H_{44}N_2O_5S$: C, 72.75; H, 6.55; N, 4.14. Found: C, 72.78; H, 6.46; N, 4.14.

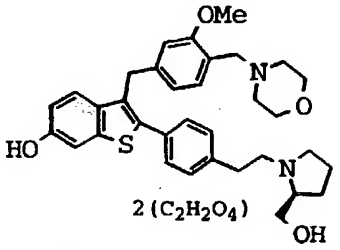
Part C. 6-Hydroxy-2-[4-[2-[1-[(*S*)-2-hydroxymethyl]-pyrrolidinyl]ethyl]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(4-morpholinyl)methyl]phenyl Ketone Dioxalate.

Following the procedure of Example 41, Part E, the salt of the hydroxy benzothiophene was obtained from the above benzyl ether as a yellowish solid in an overall 65% yield.

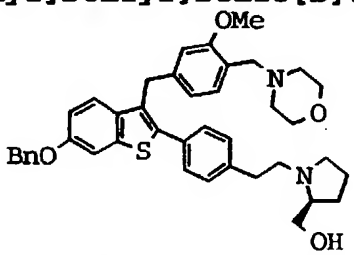
IR (KBr) 3377 (br), 3400-2500 (br), 1718, 1638, 1609 cm^{-1}; FDMS *m/e* 587 (M+1-$2C_2H_2O_4$). Anal. Calcd for $C_{34}H_{38}N_2O_5S \cdot 1.4C_2H_2O_4$: C, 62.01; H, 5.77; N, 3.93. Found: C, 61.99; H, 5.80; N, 4.12.

Example 54

Preparation of 6-Hydroxy-2-[4-[2-[1-[(*S*)-2-hydroxymethyl]pyrrolidinyl]ethyl]phenyl]-3-[3-methoxy-4-[(4-morpholinyl)methyl]benzyl]benzo[*b*]thiophene Dioxalate.



Part A. 6-Benzyloxy-2-[4-[2-[1-[(*S*)-2-hydroxymethyl]-pyrrolidinyl]ethyl]phenyl]-3-[3-methoxy-4-[(4-morpholinyl)methyl]benzyl]benzo[*b*]thiophene.



Following the procedure of Example 34, Part D, the methylene compound was obtained from the above ketone as a foam in 88% yield.

IR (neat) 3390 (br), 2955, 1600 cm^{-1}; FDMS *m/e* 663 (M+1). Anal. Calcd for $C_{41}H_{46}N_2O_4S$: C, 74.29; H, 6.99; N, 4.23. Found: C, 74.40; H, 6.97; N, 4.18.

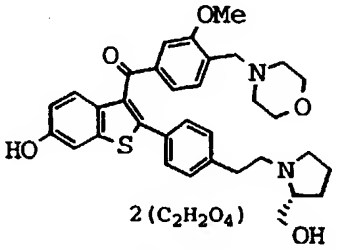
Part B. 6-Hydroxy-2-[4-[2-[1-[(*S*)-2-hydroxymethyl]-pyrrolidinyl]ethyl]phenyl]-3-[3-methoxy-4-[(4-morpholinyl)methyl]benzyl]benzo[*b*]thiophene Dioxalate.

Following the procedure of Example 41, Part E, the salt of the hydroxy benzothiophene was obtained from the above benzyl ether as a white solid in an overall 73% yield.

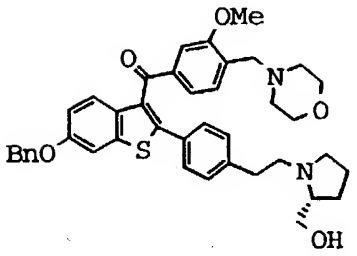
IR (KBr) 3376 (br), 3400-2500 (br), 1719, 1612 cm^{-1}; FDMS *m/e* 573 (M+1-$2C_2H_2O_4$]. Anal. Calcd for $C_{34}H_{40}N_2O_4S \cdot 1.2C_2H_2O_4$: C, 64.22; H, 6.28; N, 4.11. Found: C, 64.01; H, 6.10; N, 3.97.

Example 55

Preparation of 6-Hydroxy-2-[4-[2-[1-[(*R*)-2-hydroxy-methyl]pyrrolidinyl]ethyl]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(4-morpholinyl)methyl]phenyl Ketone Dioxalate.



Part A. Preparation of 6-Benzyloxy-2-[4-[2-[1-[(*R*)-2-hydroxymethyl]pyrrolidinyl]ethyl]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(4-morpholinyl)methyl]phenyl Ketone.



Following the procedure of Example 43, Part C, the substituted prolinol was obtained from the alcohol of Example 53, Part A and (*R*)-prolinol as a foam in an overall 48% yield.

IR (neat) 3378 (br), 2956, 1648, 1600 cm^{-1}; FDMS *m/e* 677 (M+1). Anal. Calcd for $C_{41}H_{44}N_2O_5S$: C, 72.75; H, 6.55; N, 4.14. Found: C, 72.96; H, 6.32; N, 4.20.

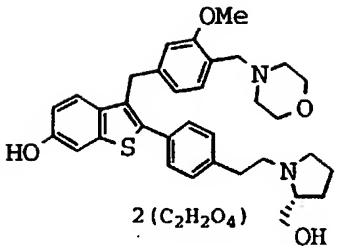
Part B. 6-Hydroxy-2-[4-[2-[1-[(*R*)-2-hydroxymethyl]-pyrrolidinyl]ethyl]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[(4-morpholinyl)methyl]phenyl Ketone Dioxalate.

Following the procedure of Example 41, Part E, the salt of the hydroxy benzothiophene was obtained from the above benzyl ether as a yellowish solid in an overall 63% yield.

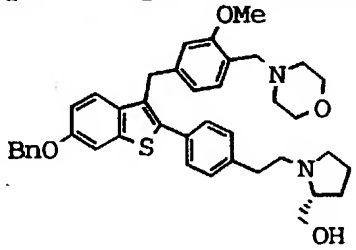
IR (KBr) 3384 (br), 3400-2500 (br), 1719, 1638, 1607 cm^{-1}; FDMS *m/e* 587 (M+1-$2C_2H_2O_4$). Anal. Calcd for $C_{34}H_{38}N_2O_5S \cdot 1.4C_2H_2O_4$: C, 62.01; H, 5.77; N, 3.93. Found: C, 61.73; H, 5.90; N, 4.14.

Example 56

Preparation of 6-Hydroxy-2-[4-[2-[1-[(*R*)-2-hydroxymethyl]pyrrolidinyl]ethyl]phenyl]-3-[3-methoxy-4-[(4-morpholinyl)methyl]benzyl]benzo[*b*]thiophene Dioxalate.



Part A. 6-Benzyloxy-2-[4-[2-[1-[(*R*)-2-hydroxymethyl]-pyrrolidinyl]ethyl]phenyl]-3-[3-methoxy-4-[(4-morpholinyl)methyl]benzyl]benzo[*b*]thiophene.



Following the procedure of Example 34, Part D, the methylene compound was obtained from the ketone of Example 55, Part A as a foam in 83% yield.

IR (neat) 3426 (br), 2955, 1600 cm^{-1}; FDMS *m/e* 663 (M+1). Anal. Calcd for $C_{41}H_{46}N_2O_4S$: C, 74.29; H, 6.99; N, 4.23. Found: C, 74.29; H, 6.98; N, 4.33.

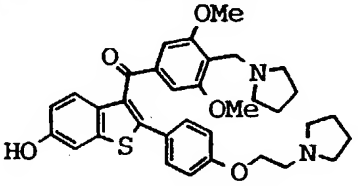
Part B. 6-Hydroxy-2-[4-[2-[1-[(*R*)-2-hydroxymethyl]-pyrrolidinyl]ethyl]phenyl]-3-[3-methoxy-4-[(4-morpholinyl)methyl]benzyl]benzo[*b*]thiophene Dioxalate.

Following the procedure of Example 41, Part E, the salt of the hydroxy benzothiophene was obtained from the above benzyl ether as a white solid in an overall 77% yield.

IR (KBr) 3401 (br), 3400-2500 (br), 1718, 1612 cm^{-1}; FDMS *m/e* 573 (M+1-$2C_2H_2O_4$). Anal. Calcd for $C_{34}H_{40}N_2O_4S \cdot 1.5C_2H_2O_4$: C, 62.79; H, 6.12; N, 3.96. Found: C, 62.68; H, 5.88; N, 4.13.

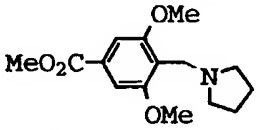
Example 57

Preparation of 3,5-Dimethoxy-4-[(1-pyrrolidinyl)-methyl]phenyl 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone.



$2(H_2C_2O_4)$

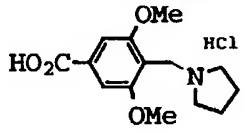
Part A. Methyl 3,5-Dimethoxy-4-[(1-pyrrolidinyl)-methyl]benzoate.



Following the procedure of Example 37, Part A, the substituted pyrrolidine was obtained from methyl 3,5-dimethoxy-4-methylbenzoate and pyrrolidine as an oil in 51% yield.

IR (KBr) 2964, 1721 cm^{-1}; FDMS *m/e* 279 (M^+). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.56; H, 7.65; N, 5.04.

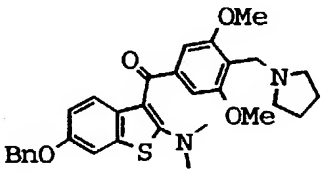
Part B. 3,5-Dimethoxy-4-[(1-pyrrolidinyl)methyl]-benzoic Acid Hydrochloride.



Following the procedure of Example 37, Part B, the acid was obtained from the above ester as a white solid in 100% yield.

^1H NMR (DMSO-d_6) δ1.80-2.00 (m, 4H), 3.00 (br s, 2H), 3.32 (br s, 2H), 3.86 (s, 6H), 4.20 (s, 2H), 7.20 (s, 2H).

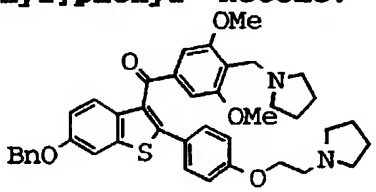
Part C. 6-Benzyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 3,5-Dimethoxy-4-[(1-pyrrolidinyl)methyl]-phenyl Ketone.



Following the procedure of Example 39, Part C, the ketone was obtained from 6-benzyloxy-2-(dimethylamino)-benzo[*b*]thiophene and the above acid as a foam in 71% yield.

IR (neat) 2957, 1625, 1601 cm^{-1}; FDMS *m/e* 530 (M^+).

Part D. 6-Benzyloxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 3,5-Dimethoxy-4-[(1-pyrrolidinyl)methyl]phenyl Ketone.



Following the procedure of Example 34, Part C, the ketone was obtained from the corresponding aryl bromide and the above ketone as a foam in 88% yield.

IR (neat) 2957, 1647, 1606 cm^{-1}; FDMS *m/e* 677 (M+1). Anal. Calcd for $C_{41}H_{44}N_2O_5S$: C, 72.75; H, 6.55; N, 4.14. Found: C, 72.55; H, 6.76; N, 4.19.

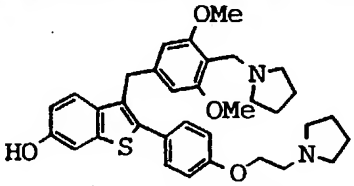
Part E. 3,5-Dimethoxy-4-[(1-pyrrolidinyl)methyl]-phenyl 6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl Ketone.

Following the procedure of Example 41, Part E, the salt of the hydroxy benzothiophene was obtained from the above benzyl ether as a yellowish solid in an overall 70% yield.

IR (KBr) 3450-2500 (br), 1720, 1643 cm^{-1}; FDMS *m/e* 587 (M+1-$2C_2H_2O_4$). Anal. Calcd for $C_{34}H_{38}N_2O_5S \cdot 2C_2H_2O_4$: C, 59.52; H, 5.52; N, 3.65. Found: C, 59.71; H, 5.78; N, 3.56.

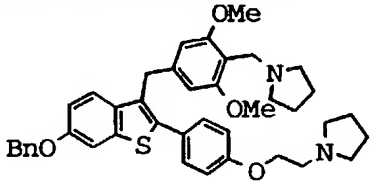
Example 58

Preparation of 3-[3,5-Dimethoxy-4-[(1-pyrrolidinyl)-methyl]benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



$2(C_2H_2O_4)$

Part A. 6-Benzyloxy-3-[3,5-dimethoxy-4-[(1-pyrrolidinyl)methyl]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene.



Following the procedure of Example 34, Part D, the methylene compound was obtained from the ketone of Example 57, Part D as a foam in 79% yield.

IR (neat) 2961, 1606 cm^{-1}; FDMS *m/e* 663 (M+1). Anal. Calcd for $C_{41}H_{46}N_2O_4S$: C, 74.29; H, 6.99; N, 4.23. Found: C, 74.48; H, 7.15; N, 4.37.

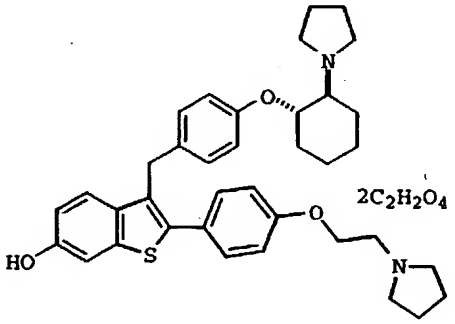
Part B. 3-[3,5-Dimethoxy-4-[(1-pyrrolidinyl)methyl]-benzyl]-6-hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene Dioxalate.

Following the procedure of Example 41, Part E, the salt of the hydroxy benzothiophene was obtained from the above benzyl ether as a white solid in an overall 71% yield.

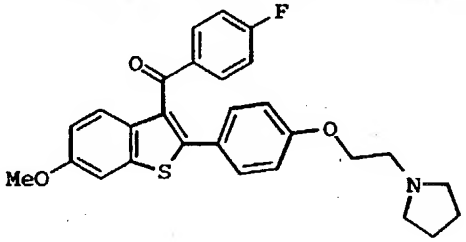
IR (KBr) 3450-2500 (br), 1721, 1609 cm^{-1}; FDMS *m/e* 573 (M+1-$2C_2H_2O_4$). Anal. Calcd for $C_{34}H_{40}N_2O_4S \cdot 2C_2H_2O_4$: C, 60.63; H, 5.89; N, 3.72. Found: C, 60.92; H, 6.11; N, 3.94.

Example 59

Preparation of (±)-6-Hydroxy-3-[4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



Part A. 6-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 4-Fluorophenyl Ketone.

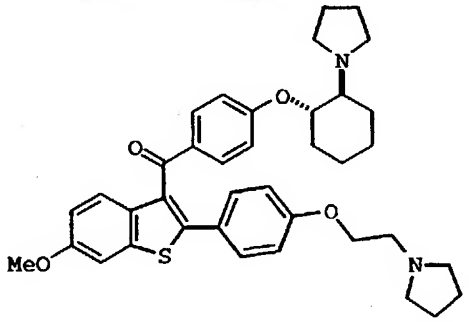


To 671.4 mg of 6-methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene (Example 1, Part B) in 10 mL of 1,2-dichloroethane was added 1.114 g of $AlCl_3$ at 0 °C, followed by dropwise addition of 0.30 mL of 4-fluorobenzoyl chloride. The deep red solution was stirred at 0 °C for 1 h and then at 0 to 15 °C for 19 h. The reaction was quenched by pouring the reaction mixture into 50 mL of ice-cold 2.0 N NaOH solution. The mixture was then extracted with 3x100 mL of EtOAc which was washed with 50 mL of H_2O and brine. Combined organic layers were dried over $MgSO_4$, concentrated, and purified by flash chromatography with 5 v/v % (10% conc

NH_4OH in MeOH) in CH_2Cl_2 to give 826.4 mg (92%) of the product ketone as viscous oil.

FDMS 475 (M^+); Anal Calcd for $C_{28}H_{26}FNO_3S$: C, 70.71; H, 5.51; N, 2.94. Found: C, 70.75; H, 5.58; N, 3.15.

Part B. (±)-6-Methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-Pyrrolidinyl)cyclohexyl]oxy]phenyl Ketone.



To a suspension of ca. 60 mg of NaH (60% oil dispersion) in 2.0 mL of freshly distilled THF was added 330.9 mg of (±)*trans*-2-(1-pyrrolidinyl)cyclohexanol in 2.0 mL of THF at room temperature. The mixture was heated at reflux for 45 min, cooled down to room temperature, and then to this was added 0.90 mL of 1.086 M of the fluoride (Part A). The mixture was heated at reflux for 24 h, cooled down, and then the reaction was quenched with 20 mL of H_2O. The mixture was extracted with 3x50 mL of EtOAc which was washed with 25 mL of brine. The combined extracts were dried over $MgSO_4$, concentrated, and purified by flash chromatography with 40:5:55 THF-Et_3N-hexanes to afford 349.9 mg (57%) of the product along with 49.0 mg (10%) of recovered fluoride.

mp 39-47 °C; FDMS 624.9 (M^+), 500.8 (base); Anal. Calcd for $C_{38}H_{44}N_2O_4S$: C, 73.05; H, 7.10; N, 4.48. Found: C, 73.01; H, 7.25; N, 4.21.

Part C. (±)-6-Hydroxy-3-[4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-

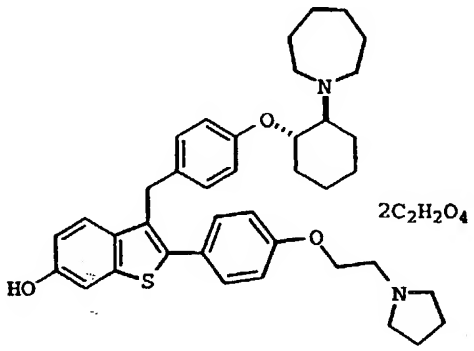
pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

The title compound was prepared in 36% yield for four steps from the ketone (Part B) by essentially following the procedures detailed in Example 21, Parts A-C.

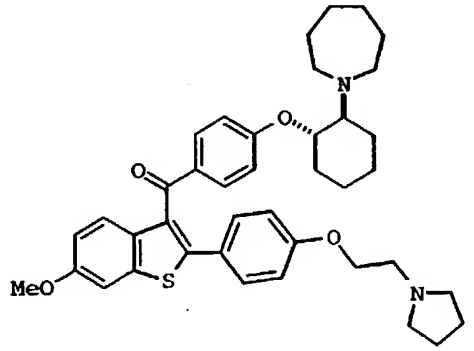
mp >105 °C (decomp?); FDMS 597.1 (M+1); Anal. Calcd for $C_{37}H_{44}N_2O_3S \cdot 2.5C_2H_2O_4$: C, 61.38; H, 6.01; N, 3.41. Found: C, 61.63; H, 5.77; N, 3.01.

Example 60

Preparation of (±)-6-Hydroxy-3-[4-[[*trans*-2-(hexahydro-1H-azepin-1-yl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



Part A. (±)-6-Methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(Hexahydro-1H-azepin-1-yl)cyclohexyl]oxy]phenyl Ketone.



The title compound was prepared in 54% yield from 6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo-[*b*]thiophen-3-yl] 4-fluorophenyl ketone and (±)-*trans*-2-(hexahydro-1H-azepin-1-yl)cyclohexanol by essentially following the procedures detailed in Example 59, Part B.

mp 43.5-51.5 °C; FDMS 653.1 (M+1); Anal. Calcd for $C_{40}H_{48}N_2O_4S$: C, 73.59; H, 7.41; N, 4.29. Found: C, 73.61; H, 7.61; N, 4.07.

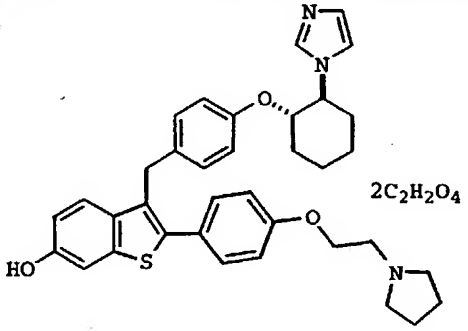
Part B. (±)-6-Hydroxy-3-[4-[[*trans*-2-(hexahydro-1H-azepin-1-yl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

The title compound was prepared in 29% yield for four steps from the ketone (Part A) by essentially following the procedures detailed in Example 21, Parts A-C.

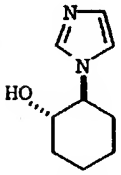
mp >114 °C (decomp?); FDMS 625.1 (M+1); Anal. Calcd for $C_{39}H_{48}N_2O_3S \cdot 2.5C_2H_2O_4$: C, 62.18; H, 6.28; N, 3.30. Found: C, 62.02; H, 6.28; N, 3.12.

Example 61

Preparation of (±)-6-Hydroxy-3-[4-[[*trans*-2-(imidazol-1-yl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



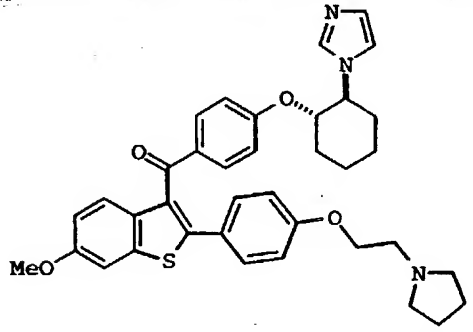
Part A. (±)-trans-2-(Imidazol-1-yl)cyclohexanol.



A mixture of 20.18 g of imidazole, 81.95 g of K_2CO_3, and 20.0 mL of cyclohexene oxide in ca. 200 mL of H_2O was stirred at room temperature for 19 h, at 100 °C (bath temp.) for 7 h, and then at room temperature overnight. The mixture was extracted with 3x500 mL of EtOAc and 500 mL of CH_2Cl_2. The organic layers were washed with 2x300 mL of H_2O and 300 mL of brine. Combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was crystallized from EtOAc to yield 8.57 g (26%) of the crystalline solid.

mp 127-131 °C; FDMS 167 (M+1); Anal Calcd for $C_9H_{14}N_2O \cdot 0.22H_2O$: C, 63.52; H, 8.55; N, 16.46. Found: C, 63.63; H, 8.30; N, 16.11.

Part B. (±)-6-Methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(Imidazol-1-yl)cyclohexyl]oxy]phenyl Ketone.



The title compound was prepared in 71% yield from 6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo-[*b*]thiophen-3-yl] 4-fluorophenyl ketone and (±)-*trans*-2-(imidazol-1-yl)cyclohexanol (Part A) by essentially following the procedures detailed in Example 59, Part B.

mp 68-78 °C; FDMS 622.4 (M+1); Anal. Calcd for $C_{37}H_{39}N_3O_4S \cdot 0.35NH_4OH$: C, 70.09; H, 6.48; N, 7.40. Found: C, 69.75; H, 6.14; N, 7.03.

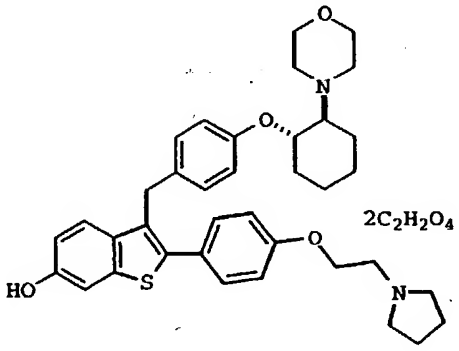
Part C. (±)-6-Hydroxy-3-[4-[[*trans*-2-(imidazol-1-yl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

The title compound was prepared in 81% yield for four steps from the ketone (Part B) by essentially following the procedures detailed in Example 21, Parts A-C.

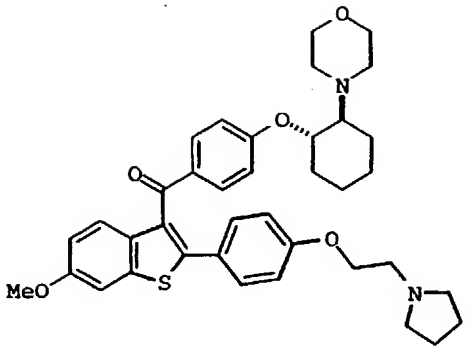
mp >103 °C (decomp?); FDMS 594 (M+1); Anal. Calcd for $C_{36}H_{39}N_3O_3S \cdot 2.1C_2H_2O_4 \cdot 1.1C_4H_8O_2$: C, 60.89; H, 5.96; N, 4.78. Found: C, 60.49; H, 5:59; N, 4.95.

Example 62

Preparation of (±)-6-Hydroxy-3-[4-[[*trans*-2-(4-morpholinyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



Part A. (±)-6-Methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(4-Morpholinyl)cyclohexyl]oxy]phenyl Ketone.



The title compound was prepared in 80% yield from 6-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo-[*b*]thiophen-3-yl] 4-fluorophenyl ketone and (±)-*trans*-2-(4-morpholinyl)cyclohexanol by essentially following the procedures detailed in Example 59, Part B.

mp 50-57 °C; FDMS 640.6 (M^+); Anal. Calcd for $C_{38}H_{44}N_2O_5S \cdot 0.14CH_2Cl_2$: C, 70.18; H, 6.84; N, 4.29. Found: C, 70.20; H, 6.82; N, 4.35.

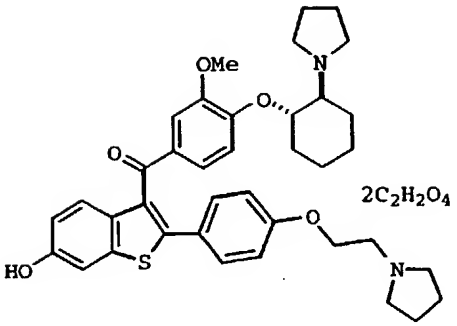
Part B. (±)-6-Hydroxy-3-[4-[[*trans*-2-(4-morpholinyl)-cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

The title compound was prepared in 72% yield for four steps from the ketone (Part A) by essentially following the procedures detailed in Example 21, Part A-C.

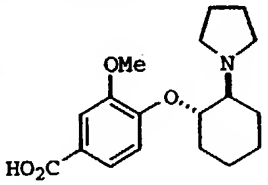
mp >110 °C (decomp?); FDMS 613.4 (M+1); Anal Calcd for $C_{37}H_{44}N_2O_4S \cdot 2.3C_2H_2O_4 \cdot 1.1C_4H_8O_2$: C, 60.26; H, 6.31; N, 3.06. Found: C, 59.88; H, 5.94; N, 3.00.

Example 63

Preparation of (±)-6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl] 3-Methoxy-4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]phenyl Ketone Dioxalate.



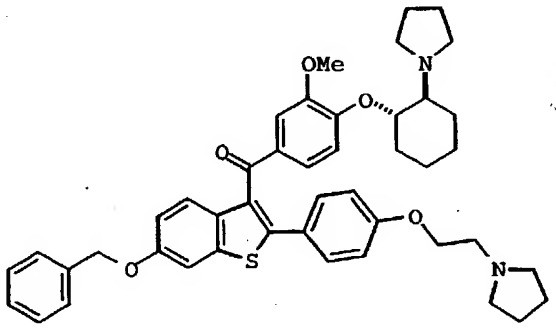
Part A. 3-Methoxy-4-[[*trans*-2-(1-pyrrolidinyl)-cyclohexyl]oxy]benzoic Acid.



The title compound was prepared in 96% for two steps from methyl vanillate similarly as described in Example 20, Parts B and C.

^{1}H NMR ($CDCl_3$) d 7.68 (m, 2H), 7.17 (d, J = 8.8 Hz, 1H), 4.80 (m, 1H), 3.88 (s, 3H), 3.63 (m, 2H), 3.35 (m, 2H), 3.11 (m, 1H), 2.35-1.25 (m, 12H).

Part B. (±)-6-Benzyloxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]phenyl Ketone.



The title compound was prepared in 43% yield for two steps from 6-benzyloxy-2-(dimethylamino)benzo[*b*]thiophene by essentially following the procedures outlined in Example 41,

Part C (but using thionyl chloride to form the acid chloride) and Example 81, Part E.

mp 50-54 °C; FDMS 731.8 (M+1); Anal. Calcd for $C_{45}H_{50}N_2O_5S$: C, 73.94; H, 6.90; N, 3.83. Found: C, 73.73; H, 6.96; N, 4.00.

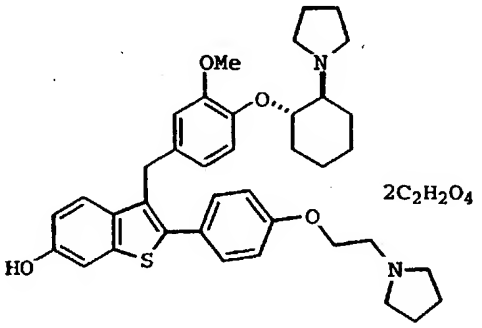
Part C. (±)-6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Methoxy-4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]phenyl Ketone Dioxalate.

The title compound was prepared in 12% yield for two steps from (±)-6-benzyloxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl [3-methoxy-4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]phenyl] ketone (Part B) by essentially following the procedures described for debenzylation and oxalate salt formation in Example 81, Part I.

FDMS 641.3 (M+1); Anal. Calcd for $C_{38}H_{44}N_2O_5S \cdot 2C_2H_2O_4$: C, 61.45; H, 5.89; N, 3.41. Found: C, 61.27; H, 5.77; N, 3.40.

Example 64

Preparation of (±)-6-Hydroxy-3-[3-methoxy-4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



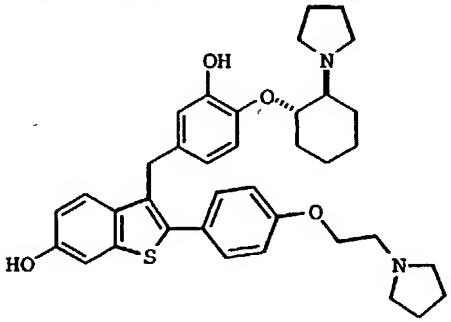
The title compound was prepared in 59% yield for four steps from (±)-6-benzyloxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 3-methoxy-4-[[*trans*-2-(1-

pyrrolidinyl)cyclohexyl]oxy]phenyl ketone (Example 63, Part B) by essentially following the procedures outlined in Example 85, Part B.

FDMS 627.3 (M+1); Anal. Calcd for $C_{38}H_{46}N_2O_4S \cdot 2C_2H_2O_4$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.73; H, 6.18; N, 3.43.

Example 65

Preparation of (±)-6-Hydroxy-3-[3-hydroxy-4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene.

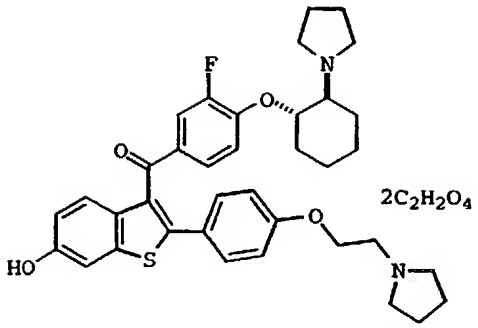


The title compound was prepared in 29% yield from (±)-6-hydroxy-3-[3-methoxy-4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]-oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]-thiophene (free base of Example 64) by essentially following the procedure outlined in Example 21, Part B.

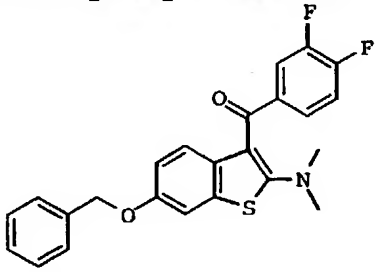
FDMS 613.3 (M+1).

Example 66

Preparation of (±)-6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Fluoro-4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]phenyl Ketone Dioxalate.



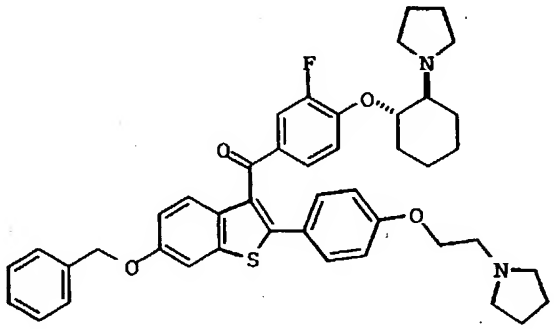
Part A. 6-Benzyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 3,4-Difluorophenyl Ketone.



The title compound (oil) was prepared in 95% yield from 6-benzyloxy-2-(dimethylamino)benzo[*b*]thiophene and 3,4-difluorobenzoyl chloride by essentially following the procedure outlined in Example 81, Part C.

FDMS 423 (M+); Anal. Calcd for $C_{24}H_{19}F_2NO_2S$: C, 68.07; H, 4.52; N, 3.31. Found: C, 68.36; H, 4.75; N, 3.37.

Part B. (±)-6-Benzyloxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Fluoro-4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]phenyl Ketone.



The title compound was prepared in 67% yield for two steps from 6-benzyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 3,4-difluorophenyl ketone (Part A) similarly as described in Example 59, Part B and Example 81, Part E.

mp 47-51 °C; FDMS 719 (M+1); Anal. Calcd for $C_{44}H_{47}FN_2O_4S$: C, 73.51; H, 6.59; N, 3.90. Found: C, 73.28; H, 6.71; N, 4.01.

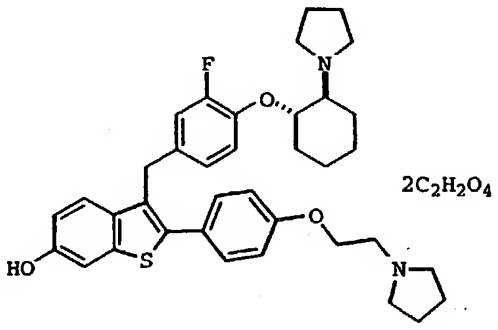
Part C. (±)-6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl] 3-Fluoro-4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]phenyl Ketone Dioxalate.

The title compound was obtained in 81% for two steps from the ketone (Part B) via debenzylation and oxalate salt formation as described in Example 81, Part I.

FDMS 629.3 (M+1); Anal. Calcd for $C_{37}H_{41}FN_2O_4S \cdot 2C_2H_2O_4$: C, 60.88; H, 5.61; N, 3.46. Found: C, 60.97; H, 5.70; N, 3.59.

Example 67

Preparation of (±)-6-Hydroxy-3-[3-fluoro-4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



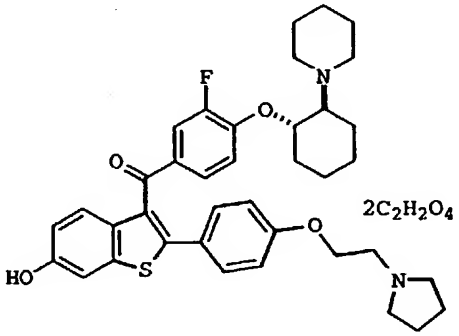
The title compound was prepared in 66% yield for four steps from (±)-6-benzyloxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophen-3-yl 3-fluoro-4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]phenyl ketone (Example 66,

Part B) using similar procedures to those of Example 85, Part B.

mp >111 °C (decomp.?); FDMS 614.8 (M+); Anal. Calcd for $C_{37}H_{43}FN_2O_3S \cdot 2C_2H_2O_4$: C, 61.95; H, 5.96; N, 3.52. Found: C, 61.81; H, 6.16; N, 3.38.

Example 68

Preparation of (±)-6-Hydroxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 3-Fluoro-4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]phenyl Ketone Dioxalate.

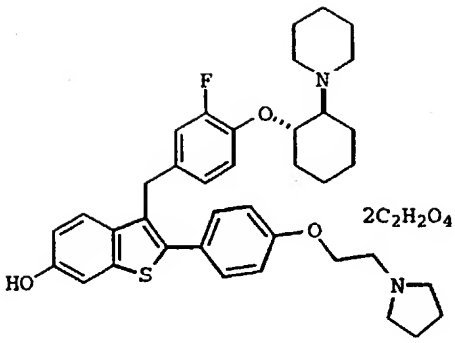


The title compound was prepared in 13% for four steps from 6-benzyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 3,4-difluorophenyl ketone (Example 66, Part A) using similar methods to those of Example 66, Parts B and C.

FDMS 643.4 (M+1); Anal. Calcd for $C_{38}H_{43}FN_2O_4S \cdot 2C_2H_2O_4$: C, 61.30; H, 5.76; N, 3.41. Found: C, 61.57; H, 5.74; N, 3.59.

Example 69

Preparation of (±)-6-Hydroxy-3-[3-fluoro-4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

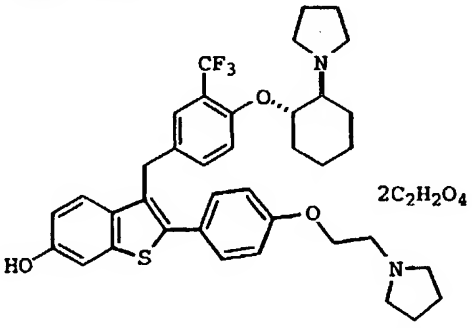


The title compound was prepared in 62% for three steps from (±)-6-benzyloxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]-benzo[*b*]thiophen-3-yl 3-fluoro-4-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]phenyl ketone (an intermediate in the preparation of Example 68) using procedures similar to those of Example 85, Part B.

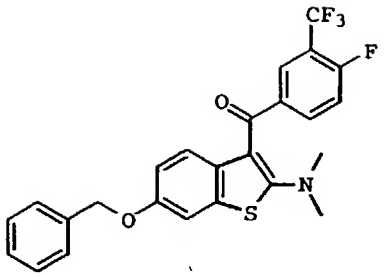
FDMS 629.4 (M+1); Anal. Calcd for $C_{38}H_{45}FN_2O_3S \cdot 2C_2H_2O_4 \cdot 1.1C_4H_8O$: C, 62.74; H, 6.56; N, 3.15. Found: C, 63.14; H, 6.27; N, 2.92.

Example 70

Preparation of (±)-6-Hydroxy-3-[4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]-3-(trifluoromethyl)-benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo-[*b*]thiophene Dioxalate.



Part A. 6-Benzyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 4-Fluoro-3-(trifluoromethyl)phenyl Ketone.



The title compound was prepared in 93% yield from 6-benzyloxy-2-(dimethylamino)benzo[*b*]thiophene and 4-fluoro-3-(trifluoromethyl)benzoyl chloride by essentially following the procedure outlined in Example 81, Part C, and Example 85, Part B.

mp 164-167 °C; FDMS 473 (M+); Anal. Calcd for $C_{25}H_{19}F_4NO_2S$: C, 63.42; H, 4.04; N, 2.96. Found: C, 63.65; H, 4.17; N, 2.81.

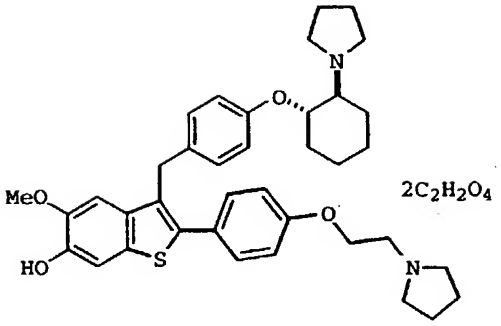
Part B. (±)-6-Hydroxy-3-[4-[[*trans*-2-(1-pyrrolidinyl)-cyclohexyl]oxy]-3-(trifluoromethyl)-benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo-[*b*]thiophene Dioxalate.

The title compound was prepared in 41% for six steps from 6-benzyloxy-2-(dimethylamino)benzo[*b*]thiophen-3-yl 4-fluoro-3-(trifluoromethyl)phenyl ketone (Part A) using similar procedures to those of Example 66, Parts B and C.

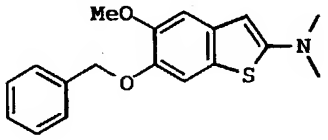
mp >124 °C (decomp?); FDMS 665.2 (M+1); Anal. Calcd for $C_{38}H_{43}F_3N_2O_3S \cdot 2C_2H_2O_4$: C, 59.71; H, 5.61; N, 3.32. Found: C, 59.48; H, 5.55; N, 3.44.

Example 71

Preparation of (±)-6-Hydroxy-5-methoxy-3-[4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



Part A. 6-Benzyloxy-2-dimethylamino-5-methoxy-benzo[*b*]thiophene.



The title compound was prepared in 17% for two steps from 4-benxyloxy-3-methoxybenzaldehyde and N,N-dimethylthioformamide using similar procedures to those of Example 81, Parts A and B.

mp 140-142 °C; FDMS 313 (M+); Anal. Calcd for $C_{18}H_{19}NO_2S$: C, 68.98; H, 6.11; N, 4.47. Found: C, 68.81; H, 6.32; N, 4.17.

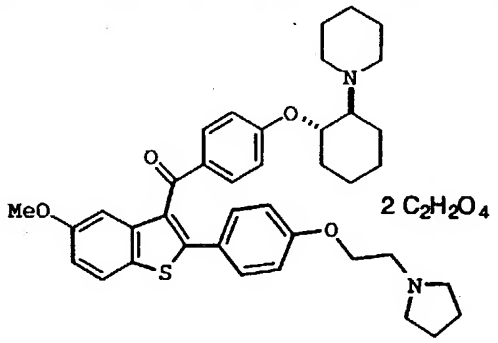
Part B. (±)-6-Hydroxy-5-methoxy-3-[4-[[*trans*-2-(1-pyrrolidinyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.

The title compound was prepared in 37% for seven steps from 6-benzyloxy-2-dimethylamino-5-methoxybenzo[*b*]thiophene (Part A) using procedures similar to those of Example 70, Parts A and B.

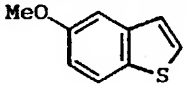
mp >100 °C (decomp?); FDMS 627 (M+1); Anal. Calcd for $C_{38}H_{46}N_2O_4S \cdot 2.4C_2H_2O_4 \cdot 0.6C_4H_8O_2$: C, 60.49; H, 6.31; N, 3.07. Found: C, 60.11; H, 6.11; N, 3.43.

Example 72

Preparation of (±)-5-Methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-Piperidyl)cyclohexyl]oxy]phenyl Ketone Dioxalate.



Part A. 5-Methoxybenzo[*b*]thiophene.

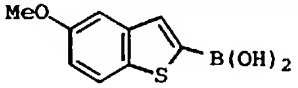


5-Bromobenzo[*b*]thiophene was prepared in quantitative yield for two steps from 4-bromobenzenethiol and bromoacetaldehyde dimethyl acetal as described in the preparation of 4- and 6-methoxybenzo[*b*]thiophene (see Example 92, Part A): mp 40-43.5 °C; FDMS 212.1 (M-1); Anal. Calcd for $C_8H_5BrS \cdot 0.10C_7H_8OS$: C, 46.01; H, 2.57; S, 15.53. Found: C, 46.19; H, 2.49; S, 15.79.

To a solution of 1.8 g of 5-bromobenzo[*b*]thiophene in 2 mL of anhydrous DMF and 1 mL of MeOH was added 686 mg of NaOMe. The mixture was heated to 110 °C (bath temp), and 121 mg of CuBr was added. The brown suspension was heated at 110 °C for ~2 h and at ~145 °C for 30 min. The reaction was quenched with ca. 50 mL of H_2O and the mixture was extracted with 100 mL of Et_2O (2x), EtOAc (1x), and CH_2Cl_2 (1x). The organic layers were washed with 50 mL of brine, combined, dried over $MgSO_4$, concentrated, and flash chromatographed with 3% Et_2O-hexanes to afford 894.5 mg (64%) of the title compound along with 168.8 mg (9.4%) of 5-bromobenzo[*b*]-thiophene.

mp 39-41.5 °C; FDMS 164.2 (M+); Anal. Calcd for $C_9H_8OS \cdot 0.11H_2O$: C, 65.04; H, 4.98; S, 19.29. Found: C, 65.07; H, 4.95; S, 18.96.

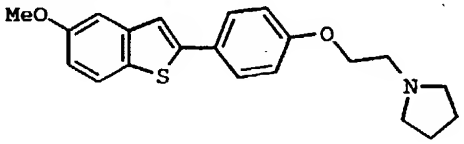
Part B. 5-Methoxybenzo[*b*]thiophene-2-boronic Acid.



The title compound was prepared in 50% yield by essentially following the procedures in Example 1, Part A from 5-methoxybenzo[*b*]thiophene (Part A).

mp 226-228 °C; FDMS 569; Anal. Calcd for $C_9H_9BO_3S$: C, 51.96; H, 4.36. Found: C, 51.85; H, 4.15.

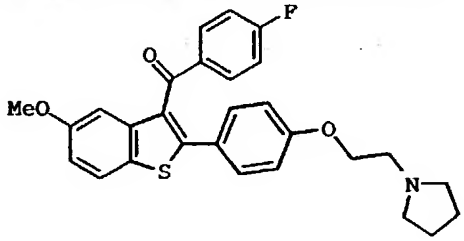
Part C. 5-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]-phenyl]benzo[*b*]thiophene.



The title compound was prepared in 47% yield by essentially following the procedures in Example 1, Part B, from 5-methoxybenzo[*b*]thiophene-2-boronic acid (Part B) and 1-(2-(4-bromophenoxy)ethyl)pyrrolidine.

mp 123-126 °C; FDMS 353 (M^+); Anal. Calcd for $C_{21}H_{23}NO_2S$: C, 71.36; H, 6.56; N, 3.96. Found: C, 71.07; H, 6.44; N, 4.01.

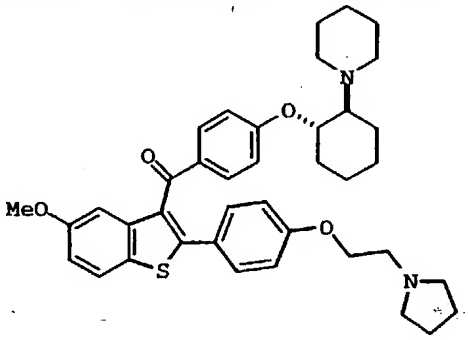
Part D. 4-Fluorophenyl 5-Methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophen-3-yl Ketone.



The title compound was prepared by essentially following the procedure detailed in Example 1, Part C, from 5-methoxy-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene (Part C) and 4-fluorobenzoyl chloride. The crude product was purified by flash chromatography (silica gel, 55:42:3 THF-hexanes-Et_3N) to afford 2.11 g (4.44 mmol, 71%) of a yellow semi-solid.

FDMS 475 (M^+); Anal. Calcd for $C_{28}H_{26}FNO_3S$: C,70.72; H, 5.51; N, 2.95. Found: C, 70.50; H, 5.49; N, 2.83.

Part E. (±)-5-Methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophen-3-yl 4-[[*trans*-2-(1-Piperidyl)cyclohexyl]oxy]phenyl Ketone.



To a slurry of NaH (530 mg, 13.2 mmol, 60% dispersion in mineral oil) in 28 mL of anhydrous DMF was added dropwise 1.61 g (8.77 mmol) of (±)-*trans*-2-(1-piperidyl)cyclohexanol (Example 20, Part A) in 7 mL of DMF at room temperature over a period of 20 min. A heat gun was applied to the reaction mixture to facilitate alkoxide formation. Slow evolution of hydrogen gas was observed. The slurry was stirred at room temperature for 1 h, and to this was added the 4-fluorophenyl ketone (2.09 g, 4.39 mmol) (Part D) in 8 ml of DMF via a cannula over 10 min period at room temperature. The slurry immediately turned reddish orange. The reaction was carried to completion by stirring overnight (18 h). The reaction was then quenched at 0 °C with slow addition of 75 mL of H_2O. The mixture was taken up in EtOAc and partitioned. The aqueous layer was extracted with EtOAc (3 x 300 mL). The

combined organic layers were dried over $MgSO_4$ after washing with 300 mL of brine and then concentrated under reduced pressure. The residue was purified by PrepLC (40:57:3 THF-hexanes-Et_3N) to afford 2.24 g (3.51 mmol, 80%) of a yellowish white foam.

mp 63-66 °C; FDMS 639 (M^+); Anal. Calcd for $C_{39}H_{46}N_2O_4S$: C, 73.32; H, 7.26; N, 4.38. Found: C, 73.03; H, 7.38; N, 4.20.

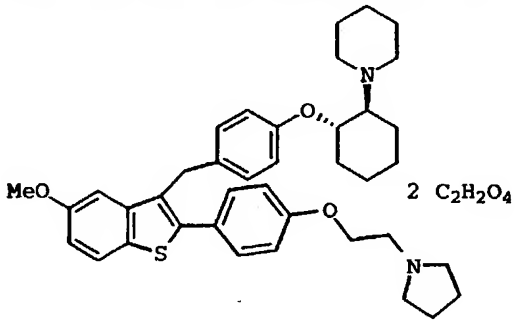
Part F. (±)-5-Methoxy-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[b]thiophen-3-yl 4-[[trans-2-(1-Piperidyl)cyclohexyl]oxy]phenyl Ketone Oxalate.

The title compound was prepared in 97% from the ketone (Part E) by essentially following the procedure outlined in Example 21, Part C.

mp 144-147 °C; FDMS 639.3 (M+); Anal. Calcd for $C_{39}H_{48}N_2O_3S \cdot 2.64C_2H_2O_4$: C, 60.67; H, 5.90; N, 3.20. Found: C, 60.66; H, 5.89; N, 3.24.

Example 73

Preparation of (±)-5-Methoxy-3-[4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



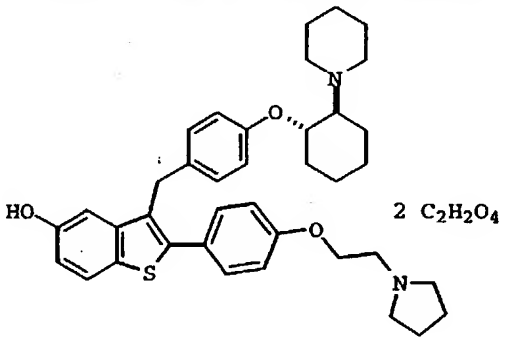
The free base of the compound was prepared in 69% yield from the ketone (Example 72, Part E) by essentially following the procedures detailed in Example 21, Part A. The title compound was prepared by essentially following the procedure outlined in Example 21, Part C.

Free base: mp 53-56 °C; FDMS 625 (M+).

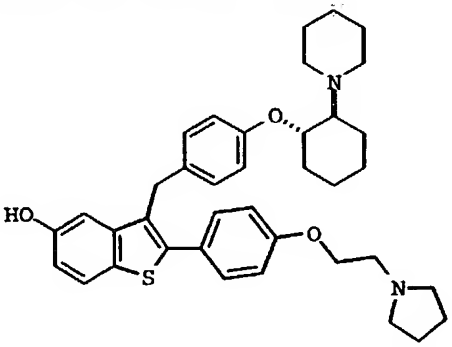
Dioxalate: mp 139-145 °C; FDMS 625 (M+); Anal. Calcd for $C_{39}H_{48}N_2O_3S \cdot 2.0C_2H_2O_4$: C, 64.16; H, 6.51; N, 3.48. Found: C, 63.88; H, 6.57; N, 3.41.

Example 74

Preparation of (±)-5-Hydroxy-3-[4-[[*trans*-2-(1-piperidyl)cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)ethoxy]phenyl]benzo[*b*]thiophene Dioxalate.



Part A. (±)-5-Hydroxy-3-[4-[[*trans*-2-(1-piperidyl)-cyclohexyl]oxy]benzyl]-2-[4-[2-(1-pyrrolidinyl)-ethoxy]phenyl]benzo[*b*]thiophene.



The title compound was prepared in 89% yield from the methoxybenzo[*b*]thiophene (free base of Example 73) by essentially following the procedures detailed in Example 21, Part B.